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ANNALS OF INTERNAL MEDICINE

VOLUME 35 DECEMBER, 1951 NUMBER 6

TERRAMYCIN THERAPY OF PNEUMONIA: CLINICAL AND BACTERIOLOGIC STUDIES IN 91 CASES *

By GEORGE G. JACKSON, M.D., *Chicago, Illinois,* THOMAS H. HAIGHT, M.D., EDWARD H. KASS,† Ph.D., M.D., *Boston, Massachusetts,* C. RAY WOMACK, M.D.,‡ *Nashville, Tennessee,* THOMAS M. GOCKE, M.D., and MAXWELL FINLAND, M.D., F.A.C.P., *Boston, Massachusetts*

THE wide variety of bacterial and other microbial agents which may be implicated in the causation of acute pulmonary infections makes such infections particularly suitable for treatment with the so-called broad spectrum antibiotics. When aureomycin, the first significant agent of this group, became available, detailed clinical and laboratory studies were carried out in this clinic in an attempt to evaluate its efficacy in pneumonias due to various etiologic agents. The results [1-4] indicated that this antibiotic was highly effective in the treatment of the various types of cases in which it was used. The present paper deals with similar studies in 91 patients with pneumonia who were treated with terramycin, another antibiotic with antimicrobial properties which closely resemble those of aureomycin.[5] A brief preliminary report of the findings in the first 25 of these patients has been presented elsewhere.[6]

PATIENTS, MATERIALS AND METHODS

Selection of Cases: All of the patients included in this study were treated on the medical wards of the Boston City Hospital between February, 1950, and June, 1951. They were all acutely ill with characteristic symptoms and

* Received for publication August 17, 1951.
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Aided by grants from the United States Public Health Service and from the Milton Fund.
† Senior Fellow in Virus Diseases, National Research Council.
‡ Post-Doctorate Research Fellow, United States Public Health Service.

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signs of acute pulmonary infection, and each had a temperature of 100° F. or higher before terramycin therapy was started. Cases classified on the basis of bacteriologic findings as pneumococcal pneumonias were included only if no sulfonamides or antibiotics had been used for this illness before the terramycin was started. Patients from whom pneumococci could not be identified before any antibiotics were given have been classified for purposes of this study as "other pneumonias," although some of them may have been due to pneumococci which were not revealed in the initial bacteriologic studies. Some of the nonpneumococcal pneumonias had failed to respond to other antimicrobial agents, usually penicillin, either before or during the first few days after the patient entered the hospital.

Clinical Studies: Each patient was observed closely and examined before and at frequent intervals after terramycin was started until the time of discharge from the hospital. Roentgenograms of the lungs were made on admission and at irregular intervals, usually twice each week, throughout the hospital stay. Leukocyte counts were done more frequently, especially early in the course of treatment. Other common laboratory tests were also done and repeated as indicated.

Bacteriologic Studies: * Blood cultures were made before terramycin was started in every patient, and were repeated when indicated, particularly in patients who remained febrile. Pleural fluids were examined by direct smear and cultures. Studies of sputum for pneumococci were carried out essentially as described for the aureomycin-treated cases.[1] In addition, attempts were made to identify the predominant and other significant pathogens in all sputum specimens. For this purpose, each sputum was cultured on the surface of blood agar and eosin-methylene blue agar aerobically, and in many instances also on chocolate agar in a candle jar. Organisms which were found in abundance were then identified. Strains of *Staphylococcus aureus* were tested for coagulase production. No attempt was made to classify streptococci except with respect to their hemolytic properties on agar containing equine blood.

During the latter part of this study, cultures were also made of the stools of some of the patients who developed diarrhea during the course of terramycin therapy. Direct smears were made of the liquid stools and were examined microscopically for organisms and cells. The feces were then cultured on the surface of blood agar and eosin-methylene blue agar and the predominant organisms were identified.

Tests for Sensitivity to Terramycin: † Many of the organisms which

* Most of the bacteriologic studies and the tests for sensitivity were carried out by Clare Wilcox and Christine Laforet. Many of the cultures were done in the bacteriologic laboratory of the Mallory Institute of Pathology by Marion E. Lamb and A. Kathleen Daly. The pneumococcus typing serums were provided in part by the Lederle Laboratories and in part by Dr. Harold W. Lyall, of the Bureau of Laboratories and Research, New York State Department of Health.

† The terramycin used for these tests and for the treatment of the patients was provided by Chas. Pfizer & Co., through the courtesy of Dr. Gladys L. Hobby.

were predominant in cultures of sputum and some which were isolated from blood or from stools were tested for sensitivity to terramycin. These tests were carried out on the surface of a series of blood agar plates containing two-fold dilutions of terramycin in an appropriate range. The blood was omitted from the agar in tests with coliform organisms. The sensitivity was defined as the minimal concentration of antibiotic on which no growth was discernible with the aid of an engraver's lens (3x) after incubation for 48 hours at 37° C.

Virus Isolations and Serologic Tests: * Attempts were made to isolate influenza viruses from throat washings of several patients in this study who were admitted during the periods of epidemic prevalence of influenza in this community (February and March of both 1950 and 1951). In addition, serum was collected at the time of admission and again at suitable intervals from all patients in whom an antecedent influenza viral infection was suspected, as well as from those in whom the possibility of a nonbacterial etiology of the pneumonia was considered. Tests for cold isohemagglutinins and for antihemagglutinins against the PR8, FM1 and Lee strains of influenza virus were carried out with these sera.

Analysis of the Cases Studied

Etiologic Classification: On the basis of the bacteriologic and clinical findings, 68 of the cases were classified as pneumococcal pneumonia; pneumococci were obtained from blood cultures as well as from sputum in 16 of these cases. The remaining 23 cases are listed in the tables for convenience under the heading "other pneumonias." Only four of these 23 cases were classified as primary atypical pneumonias from their clinical and roentgenographic findings and the failure to demonstrate any significant bacterial incitant. Two of these four patients developed cold hemagglutinins, while the other two failed to do so. The remaining 19 cases were considered to be of bacterial origin, and six of them had clinical and roentgen-ray findings consistent with the diagnosis of pneumococcal lobar pneumonia. In these six cases, however, the initial specimens of sputum were unsatisfactory, and pneumococci could be demonstrated neither in them nor in the initial blood cultures, and subsequent cultures of sputum or throat swabbings were also negative for pneumococci.

Thirteen cases were classified as nonpneumococcal bacterial pneumonias. The only or predominant organism was beta hemolytic streptococcus in four of them, *Hemophilus influenzae* in five, hemolytic and coagulase positive *Staphylococcus aureus* in one.† Both *H. influenzae* and *Staphylococcus aureus* were found in abundance in the sputum obtained prior to treatment in one case, while no significant bacterial pathogen could be isolated in two

* These studies were carried out by Mildred W. Barnes.

† Influenza virus was isolated from throat washings in this case and in one case of pneumococcal pneumonia.

cases from which only unsatisfactory sputum specimens were available prior to the onset of therapy.

Sex and Age (table 1): There was the usual predominance of males over females among the patients with pneumococcal pneumonia. These patients ranged in age from 16 to 89 years; more than three-fourths of them were over 40 years old, and more than one-fourth of them were in their seventh or later decade. Among the other cases there was a predominance of females and of patients under 40 years of age.

There were 11 Negro patients, eight with pneumococcal pneumonia and nine under 50 years of age.

Predisposing or Underlying Conditions: The relevant complicating conditions and antecedent acute respiratory infections occurring in these patients are listed in table 1. In six of the alcoholic patients, delirium tremens first developed soon after treatment was started, while two of the patients manifested this condition at the time of admission. Of the patients who had evidence of chronic cardiac disease, only one had signs of congestive failure at the time of admission, while two others developed such signs shortly after

TABLE 1

Cases of Pneumonia Treated with Terramycin

Analysis	Pneumococcal		Others		All Cases
	No.	%	No.	%	No.
All cases	68	100	23	100	91
Sex					
Male	54	79	8	35	62
Female	14	21	15	65	29
Age					
Under 40 years	15	22	14	61	29
40 to 59 years	34	50	6	26	40
60 years or older	19	28	3	13	22
Predisposing or complicating conditions					
Chronic alcoholism	12		0		12
Acute alcoholism and/or delirium tremens	8		3		11
Chronic bronchopulmonary infections	23		4*		27
Bronchial asthma	3		0		3
Cardiac disease (with failure)	7(3)		0		7
Acute undifferentiated respiratory infection					
Less than 1 week	10		4		14
1 to 2 weeks	9		1		10
More than 2 weeks	5		4		9
Proved influenza viral infection	2		1		3
Others	6†		3‡		9

* Two of these had tuberculosis, bacteriologically verified after the acute pneumonia manifestations subsided.

† Diabetes, two (one with acidosis); epilepsy, chickenpox, recent vein ligation, and recent dental extraction, one each.

‡ Diabetes with moderate acidosis, "metal fume fever" and recent dental extraction, one each.

TABLE II

Status of 91 Patients with Pneumonia at Time Terramycin Therapy Was Started

Findings	Pneumococcal		Others		All Cases
	No.	%	No.	%	No.
Day of Disease					
1	7	10	3	13	10
2	15	22	1	4	16
3	10	15	2	9	12
4	13	19	2	9	15
5	10	15	4	17	14
6	2	3	2	9	4
7–14	9	13	7	30	16
Indeterminate	2	3	2	9	4
Blood Culture					
Positive	16†	24	0	0	17
Negative	52	76	23	100	74
Pulmonary Involvement					
1 lobe	49	72	12	52	61
2 or 3 lobes (unilateral)	10	15	3	13	13
Bilateral	9	13	8	35	17
Temperature F.					
100.0–100.9	7	10	7	30	14
101.0–101.9	9	13	7	30	16
102.0–102.9	21	31	5	22	26
103.0–103.9	16	24	1	4	17
104.0 or higher	15	22	3	13	18
Leukocyte Count					
10,000 or less	11	16	6	26	17
10,000–14,900	18	26	9	39	27
15,000–19,900	16	24	6	26	22
20,000–24,900	12	18	1	4	13
25,000 or more	11	16	1	4	12
Estimated Clinical Severity					
Mild	4	6	8	35	12
Moderate	28	41	13	56	41
Severe	33	49	2	9	35
Critical	3	4	0	0	3
Previous Penicillin Therapy	0		9*	39	9

† *Staph. aureus* (but no pneumococcus) was grown from the blood of one additiona patient before terramycin was started.

* For two days in two patients, three days in three (including one who also received sulfadiazine for one week) and one each for one, four, five and nine days. One of these patients had also received chloramphenicol for two days before admission.

antibiotic treatment was instituted. The diagnosis of influenza viral infection was based on the isolation of strains of influenza A′ virus from throat washings obtained in two patients at the time of admission, while in the third patient it was based on the demonstration of a significant rise in titer of antibodies against such a strain.

Status of the Pneumonia When Terramycin Was Started (table 2): Treatment with terramycin was started on or before the fifth day of the

disease in about four-fifths of the patients with pneumococcal pneumonia and in about one-half of the other cases. Bacteremia was demonstrated before the terramycin was started only in cases of pneumococcal pneumonia; pneumococci of the same type as in the sputum were recovered from the blood in 16 cases, and the blood culture yielded *Staphylococcus aureus* in one patient whose sputum also contained some *Staphylococcus aureus*, but predominantly type 17 pneumococcus. The pulmonary lesion was limited

TABLE III

Analysis of Dosage

	Number of Cases	
	Pneumococcal	Others
Dosage regimen started, by mouth	*	
1.0 gm. every 4 hours	1†	0
1.0 gm., then 0.5 gm. every 4 hours	45	11
1.0 gm., then 0.5 gm. every 6 hours	3†§	0
0.5 gm. every 4 hours	15	11
0.5 gm. every 6 hours	3	1
Total oral dose (gm.)	*	
Less than 10	7§	1
10–19	34♯	17
20–29	19	5
30 or more	7	0
Total duration of therapy		
3 days or less	6	1
4 or 5 days	21	9
6 or 7 days	21	8
8–10 days	12	4
11–19 days	8	1
	Grams	*Days*
Average total dose		
All 91 patients	18.2	6.4
68 pneumococcal pneumonias	19.0	6.7
23 other pneumonias	15.7	5.5
84 recovered patients	18.8	6.7
7 fatal cases**	11.3	4.7

* One patient received a single intravenous dose and died before the injection was completed.

† One patient received two intravenous doses of 0.5 gm. each 12 hours apart before the first oral dose.

§ One patient was treated intravenously with 1.0 gm., followed by six doses of 0.5 gm. at 12 hour intervals before the first oral dose.

♯ Two of these patients also received 1.0 gm. intravenously.

** Excluding the patient who died during the initial intravenous dose, the average for the fatal cases was 12.8 gm. in 5.4 days.

to a single lobe in almost three-fourths of the pneumococcal pneumonias and in about one-half of the other cases. Temperature levels and leukocyte counts were generally higher before therapy was started in the pneumococcal pneumonias than in the other cases.

A general estimate was made of the severity of each case on the basis of the appearance of the patient and of all the other data obtained before terramycin was started. On this basis, only four of the 68 patients with

pneumococcal pneumonia were considered to have a mild illness; about one-half of the patients were severely ill; four were classified as critically ill, and in the rest the illness was moderate. Among the 23 other pneumonias, more than one-half of the patients were moderately ill; none was considered critical, and only two were considered to be severely ill when treatment with terramycin was started.

As already noted, none of the patients with pneumococcal pneumonia had received any sulfonamides or antibiotics before terramycin was begun. Among the remaining patients, one had received penicillin for two days and two doses of chloramphenicol; another had received sulfadiazine for a week and penicillin for three days, and seven patients had been given penicillin alone for periods varying from one to nine days. All of these patients were still acutely ill and febrile when terramycin was started.

Dosage

The doses of terramycin used in this series of cases are summarized and analyzed in table 3. The most frequent dosage regimen employed in both the pneumococcal and the other pneumonia cases was 0.5 gm. orally every four hours, a single starting dose of 1.0 gm. being used in about two-thirds of the former and in about one-half of the latter cases. Sterile preparations suitable for intravenous injection were not available during most of this study, and treatment was initiated by this route in only four patients. Some patients required a change in dosage during the course of therapy, mostly an increase of the interval between doses from four to six hours, because of failure to tolerate the drug. In the great majority of patients the total oral dose was between 10 and 30 gm., given over a period ranging from four to 10 days. The patients with pneumococcal pneumonia received somewhat more of the antibiotic than did the other patients, the average total dose in the former being 19 gm. in six and two-thirds days, as compared with an average of 15.7 gm. in five and one-half days in the latter. The average dose in the seven patients who died was more than 11 gm. in nearly five days. Excluding the patient who died during the initial intravenous injection, the other six patients who died were treated for an average of nearly five and one-half days, and received an average of almost 13 gm. of terramycin.

Effect of Terramycin on the Bacteriologic Flora

The results of the bacteriologic findings in the blood and sputum of all of the cases are summarized in table 4. The bacteriologic findings in selected cases of pneumococcal pneumonia are also shown in relation to the clinical course in figures 1 to 4.* All pneumococci that were identified in the sputum are listed in the table irrespective of their relative numbers in the

*The course and relevant findings in six additional patients have been depicted in figures 1 and 2 of the preliminary report.[6]

TABLE IV

Relevant Bacteriologic Findings in Sputum and Blood

Organism†	Number of Patients from Whom Organism Was Isolated*						
	Before Therapy	Days after Terramycin Was Started					
		1	2	3	4	5–7	8 or more
Pneumococcus							
Type 1	17 (6)	8	4	—	—	—	—
2	6 (1)	3	—	—	—	—	—
3	12 (2)	7	3	—	—	1	—
4	1 (1)	1	—	—	—	—	—
5	7 (2)	4	2	—	—	—	—
7	8 (3)	7 (1)	4	1	—	—	—
8	6 (1)	4	1	—	—	—	—
others	16	6	2	—	1	—	1
All types	73 (16)	40 (1)	16	1	1	1	1
Hemophilus influenzae#	13	7^4	4^1	—	1	—	1
Streptococcus hemolyticus	6	3	1	—	—	—	—
Staphylococcus aureus							
Initial isolation	12 (1)	3	8	8	11 (1)	9	3
After first isolation	—	5	5	7	5	8 (1)	18
Aerobacter aerogenes§	1	—	2	1	—	3	3
Escherichia coli§	—	—	—	—	—	2	1
Bacillus proteus§	—	1	—	1	1	1	5
Pseudomonas aeruginosa§	—	1	—	—	1	1	2
Klebsiella pneumoniae, type S§	—	1	1	—	—	—	—
Monilia albicans§	—	1	—	1	2	4	—
M. tuberculosis§	—	—	—	—	—	1	1
First Negative Culture for Pneumococcus after Last Positive One							
From sputum	—	21	21	15	4	1	1
From blood	—	9	5	1			

† There was one patient who received terramycin for *H. influenzae* infection after a pneumococcus had been eliminated from the sputum by penicillin therapy. Two types of pneumococci were identified in one patient and three types in another. Patients with organisms other than pneumococci are listed only when these organisms were the only or predominant ones or were found in abundance on direct culture. Streptococci which were not beta hemolytic and staphylococci which did not produce coagulase are not included here.

* Numbers in parentheses indicate patients from whom the same organism was also obtained from blood.

Superscripts indicate number of patients in whom the organism was found in large numbers for the first time.

§ First demonstration of these organisms in significant numbers.

direct cultures. Other organisms are listed only if they were present in abundance or as the only or predominant organism in direct cultures on solid media. Streptococci other than those which were beta hemolytic are not included, although alpha hemolytic strains frequently predominated in the cultures of sputum obtained after terramycin was started and at times also before this treatment was given. Staphylococci which did not produce coagulase are likewise omitted from this table.

With a single exception, all of the pneumococci were obtained from cases classified as pneumococcal pneumonias. Among the remaining organisms

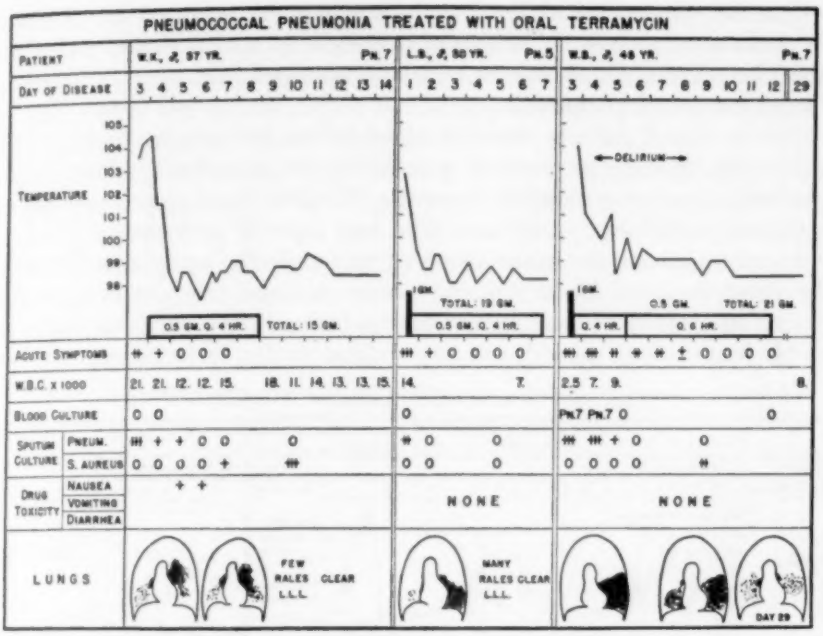
PNEUMOCOCCAL PNEUMONIA TREATED WITH ORAL TERRAMYCIN
PATIENT
W.K., ♂, 57 YR.
Pn. 7
L.S., ♂, 50 YR.
Pn. 5
W.B., ♂, 48 YR.
Pn. 7
DAY OF DISEASE
TEMPERATURE
DELIRIUM
1 GM.
TOTAL: 15 GM.
0.5 GM. Q. 4 HR.
TOTAL: 19 GM.
0.5 GM. Q. 4 HR.
0.5 GM.
TOTAL: 21 GM.
Q. 4 HR.
Q. 6 HR.
ACUTE SYMPTOMS
W.B.C. x 1000
BLOOD CULTURE
SPUTUM CULTURE
PNEUM.
S. AUREUS
DRUG TOXICITY
NAUSEA
VOMITING
DIARRHEA
NONE
NONE
LUNGS
FEW RALES CLEAR L.L.L.
MANY RALES CLEAR L.L.L.
DAY 29

FIG. 1.

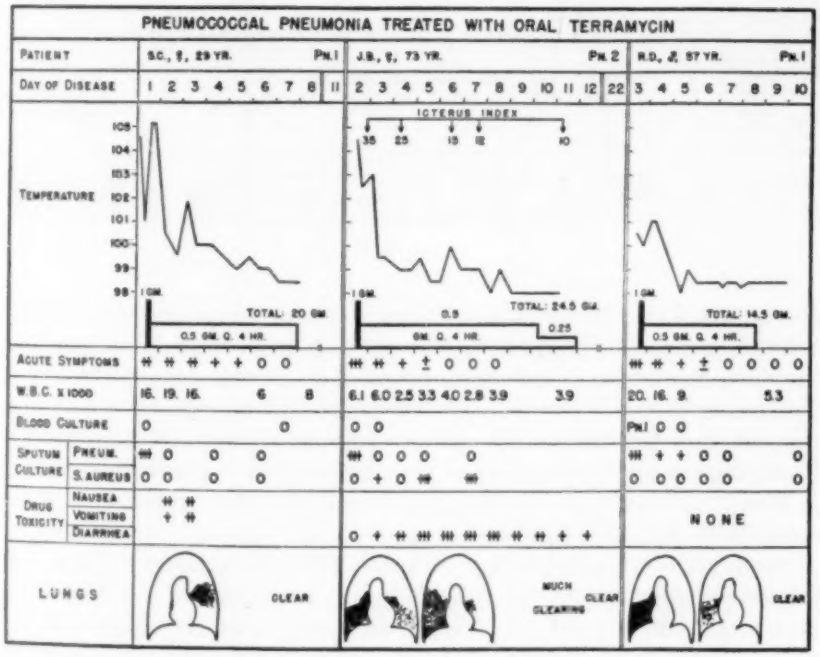
PNEUMOCOCCAL PNEUMONIA TREATED WITH ORAL TERRAMYCIN
PATIENT
S.C., ♀, 29 YR.
Pn. 1
J.B., ♀, 73 YR.
Pn. 2
R.D., ♂, 57 YR.
Pn. 1
DAY OF DISEASE
TEMPERATURE
ICTERUS INDEX
35 25 15 12 10
1 GM.
TOTAL: 20 GM.
0.5 GM. Q. 4 HR.
TOTAL: 24.5 GM.
0.5
6M. Q. 4 HR.
0.25
TOTAL: 14.5 GM.
0.5 GM. Q. 4 HR.
ACUTE SYMPTOMS
W.B.C. x 1000
BLOOD CULTURE
SPUTUM CULTURE
PNEUM.
S. AUREUS
DRUG TOXICITY
NAUSEA
VOMITING
DIARRHEA
NONE
LUNGS
CLEAR
MUCH CLEARING
CLEAR
CLEAR

FIG. 2.

found in the sputum before terramycin was started, seven of the 13 strains of *H. influenzae,* two of six strains of hemolytic streptococci, and all but two of the 12 strains of *Staph. aureus* were also obtained from sputum of patients with pneumococcal pneumonia.

Positive blood cultures were obtained before terramycin treatment was started only among the cases of pneumococcal pneumonia. Pneumococci of various types were obtained from the blood in 16 of these cases and, in one patient with lobar pneumonia who had type 17 pneumococci in abundance in the sputum, the initial blood culture yielded *Staphylococcus aureus.* Only three positive blood cultures were obtained after terramycin was started; one yielded a type 7 pneumococcus from a blood obtained on the day after terramycin was started, and two yielded strains of hemolytic *Staphylo-*

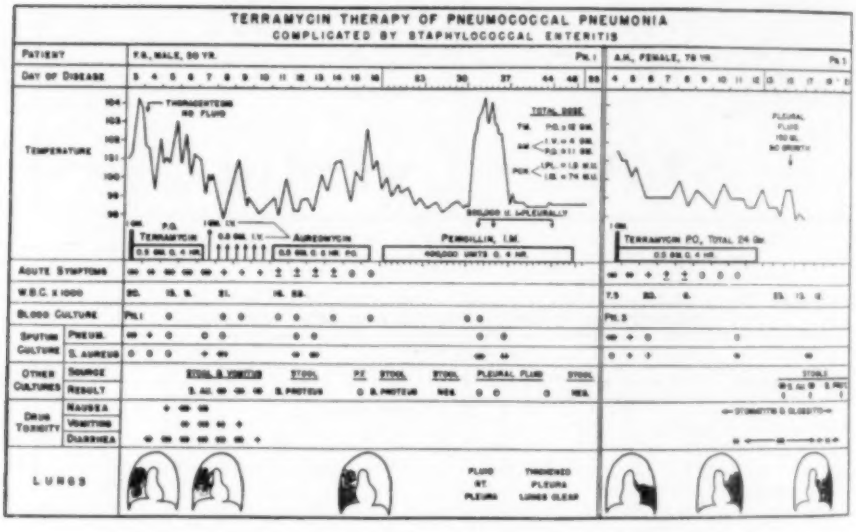

FIG. 3.

coccus aureus from blood obtained after four and six days, respectively, of terramycin therapy. Both of the latter were from cases of pneumococcal pneumonia, one a type 11 case with negative blood cultures prior to therapy, and the other a type 7 case in which the initial blood cultures were positive for this type of pneumococcus. Both of these patients (cases 67 and 80) were having severe diarrhea at the time the staphylococci were grown from their blood cultures, and the same organism was also present in abundance in cultures of their diarrheal stools.

Pneumococci were cleared quite rapidly from the sputum. Thus, on the day following the institution of terramycin, pneumococci could be demonstrated in sputum from 40 of 61 patients studied, and on the second day in 16 of 58 patients with pneumococcal pneumonia whose sputum was cultured.

Thereafter, sputum studies yielded pneumococci from only four patients, one each on the third, fourth, fifth and twelfth days, respectively, after terramycin was started. Hemolytic streptococci also were demonstrated in only one patient after the second day of terramycin therapy, and no strains were found for the first time after terramycin was started.

Strains of *H. influenzae* were found in cultures of sputum obtained before terramycin was started in 13 patients, and they were demonstrated in abundance for the first time in five additional patients in sputum obtained after one to four days of this treatment. These organisms could no longer be demonstrated in specimens of sputum obtained after from one to six days of terramycin therapy in 11 of these 18 patients, and in most of the remain-

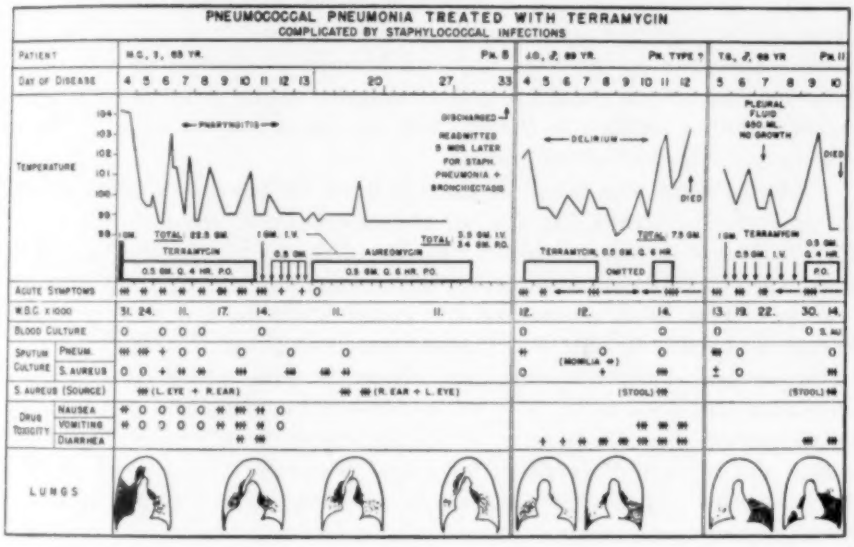

FIG. 4.

ing patients no follow-up cultures were made. In only two patients did *H. influenzae* persist in the sputum after four or more days of treatment.

Other organisms, however, became abundant or predominant in the sputum of increasing numbers of patients. Thus, strains of *Staphylococcus aureus* were found to be predominant in the sputum for the first time after terramycin was started in 48 patients. Coliform organisms and Monilia likewise appeared as the predominant organisms only during terramycin therapy. However, in most of the patients in whom *Staphylococcus aureus* first appeared in large numbers in the sputum during the course of treatment with terramycin, these strains persisted throughout the period of observation.

Pleural fluids were available for culture in 12 patients with pneumococcal pneumonia. The first specimen was obtained before treatment was started

in three of these patients; in one it yielded a type 1 and in the second a type 5 pneumococcus, while in the third it was sterile. Further thoracenteses were required only in the first of these patients, and the fluids obtained on the ninth and fifteenth days in that case were both sterile. Pneumococcus type 3 was obtained from pleural fluid post mortem in the patient who died during the initial intravenous injection of terramycin. In the remaining eight patients, all specimens of pleural fluid were sterile.

Cultures of the urine were made in three patients. One of them had pyuria before terramycin was started, and a culture of urine obtained at that time yielded *A. aerogenes* and *Ps. aeruginosa;* during and after treatment, the cultures of urine in this patient yielded *A. aerogenes* and *B. proteus.* The other two patients developed pyuria during the course of terramycin therapy. Specimens of urine obtained in one of these patients before terramycin was started and again two days later were sterile, but *B. proteus* and Monilia appeared on the third day and Monilia predominated in all subsequent specimens. In the third patient, cultures of the urine were made only during and after terramycin therapy and all yielded coagulase positive strains of hemolytic *Staphylococcus aureus.*

Cultures were also made of the stools of 18 patients while they were having watery diarrhea and in some of them also after the diarrhea stopped. The results are shown in table 5. In one of these patients, the only culture made was of a stool obtained before terramycin was started and that yielded a normal fecal flora. Some of the cultures obtained during terramycin therapy or soon after that was stopped were overgrown by *B. proteus.* Of major interest, however, was the frequency with which *Staphylococcus aureus* was obtained as the only or predominant organism in the stools during the period of active diarrhea which accompanied the terramycin administration and sometimes persisted for a few days after the drug was stopped. Direct smears of many of these stools revealed overwhelming numbers of gram-positive cocci, many red blood cells, a few other cells and some debris, but no other types of bacteria could be discerned. *Staphylococcus aureus* was also demonstrated in pure culture or as the predominant organism in sputum obtained at the same time from these patients; it was also obtained from the blood of two patients and from the urine in one patient.

Sensitivity of the Organisms to Terramycin

Tests for terramycin sensitivity were done with 116 strains isolated from sputum or blood. Three of the pneumococcal strains were obtained from blood cultures, while all of the other organisms tested were strains which were found in pure culture or as the predominant organism in sputum. The coliform organisms and most of the staphylococcal strains were from specimens of sputum obtained during terramycin therapy or soon after this treatment was stopped; the others were obtained before therapy was instituted. The results are shown in table 6.

TABLE V

Results of Cultures of Stools from Patients with Pneumonia Who Were Treated with Terramycin

Case Number	Number of Days Terramycin Was Given	Day Stool Obtained		Predominant Organism in Stool Cultures
		After Terramycin Started	After Diarrhea Started	
4	12	0	4	Normal flora.
14[a]	4	5	4	*Staph. aureus* (pure).
		6	5	*Staph. aureus* (pure), also in vomitus.
		9	8	*B. proteus* (no staph.).
		16	15	Overgrown by *B. proteus*.
		25	24	Normal flora.
		53	52	Normal flora.
34	8	12	5	Normal flora (4 specimens).
36	9	5	2	Normal flora.
37	7	3	2	*Staph. aureus* (pure).
		5	4	*Staph. aureus*, *Str. fecalis*.
		7	6	*Staph. aureus* (pure).
42	4	1	1	Normal flora.
		2	2	Normal flora.
49	4	5	2	*Staph. aureus*.
		6	3	*Staph. aureus* (pure), also in vomitus.
		8	5	*Staph. aureus*, normal flora.
53[b]	7	7	6	*Staph. aureus* (pure).
54	4	4	1	Overgrown by *B. proteus*.
		5	2	*Staph.* overgrown by *B. proteus*.
55	6	2	2	*Staph. aureus*.
		7	7	Overgrown by *B. proteus*.
64	5	10	5	Overgrown by *B. proteus*.
65	4	4	3	*Staph. aureus*, *Str. fecalis*.
66	8	10	4	*Staph. aureus* (pure).
		13	7	*Staph. aureus*.
67[c]	6	6	2	*Staph. aureus*, *Str. fecalis*.
68	9	1	1	*Staph. aureus* (nearly pure).
		4	4	*Staph. aureus*, *B. proteus*.
		5	5	*Staph. aureus* (pure).
		6	6	*Staph. aureus* (pure).
		8	8	*Staph. aureus*, *B. proteus*.
69	7	7	4	*Staph. aureus*.
		20	17[d]	Overgrown by *B. proteus*.
80	7	3	2	Monilia, *Staph. aureus*[e]
83	9	2	½	Normal flora.
		3	1	Monilia, *B. proteus*.
		4	2½	Monilia.

[a] Patient F. G., fig. 3, diarrhea lasted seven days.
[b] Patient J. O., fig. 4, terramycin omitted three of the seven days.
[c] Patient T. G., fig. 4, *Staph. aureus* in blood culture on same day.
[d] Four days after diarrhea stopped. Urine yielded *Staph. aureus* in pure culture on two occasions.
[e] *Staph. aureus* grown from blood culture two days later.

The different organisms varied widely in their sensitivity to terramycin, and there were also fairly marked differences in sensitivity among strains of the same species. In general, the strains of pneumococci, streptococci and *H. influenzae* were quite sensitive to terramycin, most of the pneumococcal strains being highly sensitive. Some of the strains of coliform organisms were only moderately sensitive, while the majority of them were moderately or markedly resistant. The results with the staphylococcal strains are of particular interest. Six of nine strains of staphylococci isolated before terramycin was started and one of nine obtained during the course of this therapy may be considered moderately sensitive; all of the others, including 14 strains isolated after terramycin was stopped, were moderately or highly resistant. In addition to those shown in the table, four strains of *Staphylococcus aureus* isolated from diarrheal stools during terramycin therapy were also tested for terramycin sensitivity. Three of these strains were highly resistant, while one was sensitive to 200 micrograms of terramycin per milliliter.

TABLE VI

Terramycin Sensitivity of 116 Strains Isolated from Sputum or Blood

Minimal Complete Inhibiting Concentration, Micrograms per Milliliter	Number of Strains											
										Staph. aureus		
										Relation to Treatment		
	Pneumococcus	*H. influenzae*	*Str. hemolyticus*	*Str. viridans**	*A. aerogenes*	*E. coli*	*B. proteus*	*Ps. aeruginosa*	*Kl. pneumoniae*	Before	During	After
0.1	2	—	—	—	—	—	—	—	—	—	—	—
0.2	1	—	—	—	—	—	—	—	—	—	—	—
0.4	12	1	—	—	—	—	—	—	—	—	—	—
0.8	14	—	1	—	—	—	—	—	—	—	—	—
1.6	17	1	—	1	—	—	—	—	—	—	—	—
3.1	3	3	1	1	—	—	—	—	—	1	—	—
6.3	3	2	—	—	—	—	—	—	—	4	1	—
12.5	1	1	—	—	—	1	—	—	—	—	—	—
25.	1	1	—	—	2	—	—	—	1	1	—	—
50.	—	—	—	1	—	1	—	—	—	—	—	—
100.	—	—	—	—	2	—	—	1	—	—	—	1
200.	—	—	—	1	—	—	1	—	—	—	1‡	—
400.	—	—	—	—	—	—	2	—	—	—	—	—
800.	—	—	—	—	—	1	3	—	—	1	3	2
>800.	—	—	—	—	—	—	—	—	—	2	4	11
Number Tested	54	9	2	4	4	3	6	1	1	9	9	14

* Organism isolated as the only or predominant one in the sputum before terramycin was started.

‡ Four additional strains which were isolated from stools obtained during treatment were also tested; one was inhibited by 200μg. per ml. and the other three grew profusely in 800μg. per ml.

Clinical Results

An analysis of the effect of terramycin on some of the major aspects of the clinical course in all of the patients is given in table 7. The results in the pneumococcal pneumonias are listed separately in this table and these will be considered first.

Results in Patients with Pneumococcal Pneumonia (figures 1 to 4): The immediate effect of terramycin on the fever and on the toxemia and other manifestations of active acute infection was generally favorable and quite prompt in most of the patients with pneumococcal pneumonia. In 48 of the 62 patients who recovered and also in five of the six who died (or 78 per cent of all the patients in this group), there was a decline in temperature to 100° F. or less within 48 hours after the first dose of terramycin was given. In most of these patients, this fall in temperature was accompanied or followed quite promptly by evidence of appreciable improvement

Table VII

Effect of Terramycin on the Clinical Course in 91 Patients with Pneumonia

Analysis*	Number of Cases	
	Pneumococcal	Others
A. First major sustained drop in temperature		
24 hours or less	28	10
25 to 48 hours	20	7
49 to 72 hours	6	2
Fourth day or later	8	3
B. Total duration of fever (over 99.4° F.)		
24 hours or less	11	6
25 to 48 hours	17	6
49 to 96 hours	10	3
5 to 7 days	12	7
8 days or more	12	0
C. Major sustained improvement in symptoms		
24 hours or less	19	13
25 to 48 hours	24	4
49 to 96 hours	13	3
Fifth day or later	6	2
D. Essentially complete symptomatic improvement		
48 hours or less	7	3
49 to 96 hours	21	6
5 to 7 days	20	10
8 to 14 days	8	3
15 days or more	6	0
E. Lungs essentially clear to physical and/or roentgen-ray examination		
7 days or less	18	10
8 to 14 days	16	5
15 to 28 days	5	2
Signs still present at last examination		
Fifth to eighth day	13	4
14th to 21st day	4	1
28th day or later	6	0

TABLE VII—*Continued*

Analysis*	Number of Cases: Pneumococcal	Others
F. Complications		
Pleural effusion‡	12 (2)	0
Atelectasis	6	0
Delayed resolution	5	1
Staphylococcal enteritis†	9 (2)	4
Other staphylococcal infections		
Pneumonia, otitis media and conjunctivitis 1	1	0
Pneumonia 3	3 (2)	0
Pyelonephritis 1	0	1
Misc. (otitis media 1, jaundice 2, cardiac failure 2, enteritis (Monilia) with rectovesical fistula, fracture during delirium 1)	6 (2)	1 (1)
G. Days of hospitalization		
7 or less§	13 (4)	4
8 to 14	27 (2)	9 (1)
15 to 21	13	5
22 to 28	7	4
29 or more	8	1
Averages—Recovered Cases: 62 Pneumococcal 17.0 days		
22 Others 13.6 days		
Fatal Cases: 6 Pneumococcal 5.8 days		
1 Other 14.0 days		
H. General estimate of benefit from terramycin		
Excellent	19	6
Moderate or good	30	9
Equivocal	11	4
No effect (recovered)	2	3
Died	(6)	(1)

* Only the patients who recovered are considered in sections A-E; in the others the numbers of fatal cases are shown in parentheses. See also tables 8 and 9.

‡ The pleural effusions were all sterile except before terramycin was started in two patients and at post mortem in the patient who died during his first dose.

† In two patients, including one who died, the staphylococcus was also recovered from the blood.

§ Includes three who left the hospital against advice during first week.

in such features as delirium, dyspnea, cyanosis, sweating, severe pleuritic pain and other manifestations of acute infection.

Complete subsidence of fever and symptomatic recovery occurred less regularly and more slowly. Thus, among the patients who recovered, 24 had some fever persisting for five days or more, and half of these patients continued to have an elevated temperature for more than a week after terramycin was started. Symptoms of active infection persisted for five days or longer in more than half of the patients who recovered, and in 14 of these patients such symptoms persisted for more than a week after initiating terramycin therapy.

The rate of clearing of the lungs was difficult to ascertain with assurance in some of the patients because of the discrepancies between the physical and roentgen-ray findings, and because roentgenograms were made only at irregular intervals in many of the patients. There were only 34 patients

whose lungs were observed to clear within two weeks after terramycin therapy was started and while they were still in the hospital. In at least 15 other patients who recovered, there was definite evidence of persistence of significant amounts of involvement of the lungs for more than two weeks after treatment with terramycin was initiated.

The most common complication of the original pulmonary infection in these cases was an effusion into the pleural cavity. As already mentioned, however, bacteriologically proved infection of the pleural fluid was found in only two patients before treatment was instituted, and post mortem in one patient who died while therapy was being started. All of the other pleural fluids which were examined were sterile, but the effusions were accompanied by fever and leukocytosis and in most patients also by systemic symptoms. Atelectasis in the affected lobes occurred in six patients, and five others were considered to have "delayed resolution" as evidenced by the persistence of physical and roentgenographic evidence of pulmonary infiltrations for more than four weeks. Some of the patients with these two complications also had pleural effusions. Other complications of the original infection were less frequent, as indicated in table 7.

The most frequent and significant complications, however, were the superinfections with hemolytic and coagulase positive strains of *Staphylococcus aureus*. Definite involvement of the lungs with this organism occurred in four patients, one of whom also had staphylococcal otitis media and conjunctivitis. There were nine patients who developed severe diarrhea during terramycin therapy, and cultures of the watery stools yielded *Staphylococcus aureus* as the only or predominant organism. Most of these patients had some blood and pus cells in these stools, and in some of them definite mucosal ulcerations were seen on proctoscopic examination. The diarrhea cleared soon after treatment was stopped in some of the patients, but in others it persisted with undiminished intensity for several days.

The total period of hospitalization sometimes depended on circumstances other than the suitability of the patient for discharge, but except in the occasional case it reflects in a general way the time when the patients who recovered were considered fit for ambulatory self-care. About three-fourths of the patients who recovered were discharged from the hospital within three weeks, and only eight (or 13 per cent) required more than four weeks of hospitalization. The average hospital stay of all the 62 patients who recovered was 17 days. Except for the patient who died soon after treatment was started, the deaths occurred between the fifth and ninth days in the hospital.

Taking all factors into account, a general estimate was made of the benefit attributable to terramycin in these cases. The effect of the antibiotic was considered to be excellent, good or moderately good in 49, or 72 per cent of the 68 cases of pneumococcal puneumonia. Such cases are illustrated in figures 1 and 2. In 11 patients of this group the effect of the

antibiotic was considered to be equivocal, while no benefit whatever could be attributed to the terramycin in two of the patients who recovered. Six patients with pneumococcal pneumonia died (9 per cent); their cases will be considered separately. Some of the less favorable results are illustrated in figures 3 and 4.

Results in Other Pneumonias: On the whole, the results in the patients who had pneumonia which was not classified as pneumococcal were somewhat better than in those with pneumococcal pneumonia. Only three of the 22 patients who recovered failed to show a decrease in temperature to 100° F. or lower within the first three days after terramycin was started, and none of them had fever persisting for more than a week. Major improvement in symptoms occurred in all but two of the patients within the first four days after terramycin was started, and symptoms of active infection persisted for more than a week in only three patients, but in none of them did these symptoms continue after the second week. The lungs were essentially clear to physical and roentgen-ray examination during the first week in 10 patients and during the second week in five additional patients. Definite evidence of persistence of pulmonary lesions for more than two weeks was obtained in only three of the patients who recovered.

Complications of the primary pulmonary infection were notably few. Only one patient had delayed resolution with pulmonary involvement persisting for more than four weeks. There were, however, other superinfections complicating the disease in five patients who recovered, and the staphylococcus was implicated in each instance. Four of these patients had severe enteritis, with essentially pure cultures of *Staphylococcus aureus* obtained from the diarrheal stool; the fifth had a urinary tract infection with pyuria, and the same organism was isolated from the urine. Diarrhea with Monilia in the stools and the development of a rectovesical fistula featured the only fatal case in this group.

The period of hospitalization was generally shorter in this group than in the pneumococcal cases. Five of the recovered patients were hospitalized for more than three weeks, and only one of them for more than four weeks. The average hospital stay in all the patients who recovered was about 13.5 days, or about three and one-half days less than for the patients with pneumococcal pneumonia. This difference is accounted for, in large measure, by the longer stay of the patients in the latter group who had complications.

In the general evaluation of the benefit attributable to terramycin in these cases, it is best to consider the patients in groups according to what was considered to be the etiology of the pulmonary infection. The cases have therefore been tabulated according to such a classification, and the estimated benefit in each etiologic group is indicated in table 8. The patients with primary atypical pneumonia which was probably of viral etiology and those with lobar pneumonia which was probably pneumococcal all showed either an excellent or a good response to the terramycin therapy. The

same was true of three of the four patients with hemolytic streptococcal pneumonia. The patient with *Staphylococcus aureus* pneumonia and one of the five whose pneumonia was considered to be due to *H. influenzae* also responded favorably. In the remaining patients, the results of terramycin therapy were considered to be equivocal or no benefit could be attributed to this treatment.

TABLE VIII

Estimate of Beneficial Effects of Terramycin in 23 Miscellaneous Cases of Pneumonia Arranged According to Their Probable Etiology

Etiology	Number of Cases	Estimate of Beneficial Effect				
		Excellent	Good	Equivocal	None	Died
Virus (?)—Primary atypical pneumonia	4	3	1	—	—	—
Probably pneumococcus—Lobar pneumonia	6	1	5	—	—	—
Streptococcus hemolyticus	4	2	1	1	—	—
Hemophilus influenzae	5	—	1	1	3	—
Staphylococcus aureus	1	—	1	—	—	—
H. influenzae and *Staph. aureus*	1	—	—	1	—	—
Probably bacterial—Organism not determined	2	—	—	1	—	1
All Cases	23	6	9	4	3	1

Effect on Leukocyte Count: The changes in the numbers of circulating leukocytes which occurred during and after terramycin therapy are of special interest since, within limitations, they reflect the course of the inflammatory processes in the patients. The results of the total leukocyte counts in all of the patients are therefore considered separately. These counts have been analyzed in relation to the time terramycin therapy was started, as shown in table 9.

TABLE IX

Résumé of Total Leukocyte Counts in 91 Patients with Pneumonia Who Were Treated with Terramycin

Leukocyte Count per cu. mm.	Before Therapy		Days after Terramycin Therapy Was Started															
			1		2		3		4		5		6–7		8–10		11 or More	
	No.	%	No.*	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Less than 8,000	11	12	6	11	9	19	12	32	10	26	7	23	9	24	10	25	5	10
8,000–10,900	9	10	9	17	11	23	7	18	12	32	6	20	9	24	9	22.5	21	43
11,000–12,900	13	14	5	9	12	25	9	24	5	13	5	17	4	11	4	10	10	20
13,000–15,900	18	20	9	17	7	14	7	18	8	21	7	23	11	30	9	22.5	9	19
16,000 or more	40	44	25	46	9	19	3	8	3	8	5	17	4	11	8	20	4	8
Totals	91	100	54	100	48	100	38	100	38	100	30	100	37	100	40	100	49	100

* Number of patients in whom counts were done and per cent of those done on the specified days.

There were 20 patients, including 12 with pneumococcal pneumonia with counts of less than 11,000 before terramycin was started. The major decline in the proportion of patients with significant leukocytosis (counts of 13,000 or more) occurred during the second and third days after terramycin was started. After that time, moderate leukocytosis occurred or persisted in a significant proportion of cases. Complications of the underlying pneumonia accounted for only a minor part of these cases. Thus, the 30 patients in whom leukocyte counts were done on the fifth day included only five with postpneumonic complications, only two of the latter having counts of 13,000 or more. Most of the patients in whom leukocytosis recurred or

TABLE X

Untoward Effects Attributable to Terramycin Among 91 Patients with Pneumonia

Toxicity	Number of Patients	Per Cent
None	38	42
Nausea only	4	4
Vomiting and nausea	12§	13
Diarrhea, vomiting and nausea	17*	19
Staph. aureus predominant in fecal culture (and vomitus in 2 cases)	7	9
Diarrhea without vomiting	20†	22
Staph. aureus predominant in fecal culture	5	6
Monilia predominant in stool	1#	1
Drug rash	1	1
Stomatitis and glossitis	2	2
Nitrogen retention	4	4
Severity necessitated reduction in dose	8	9
Severity necessitated changing to another agent (aureomycin or penicillin)	10	11

* Includes the patient who had a drug rash and three of those who developed nitrogen retention.

† Includes the two patients who developed stomatitis and glossitis.

§ Includes one of the patients who developed nitrogen retention.

This patient developed bloody diarrhea and, terminally, a fecal fistula and nitrogen retention.

persisted after the third or fourth day of terramycin therapy had gastrointestinal symptoms from the antibiotic and/or superinfections, and most of the latter were staphylococcal infections.

TOXICITY OF TERRAMYCIN

The significant untoward effects attributable to terramycin in this study and the frequency of their occurrence are shown in table 10. Some toxic effects, excluding mild nausea or anorexia, were manifested by 58 per cent of the patients. There were nine different lots used in these cases and some toxicity was observed from each of the lots. The gastrointestinal effects, and particularly diarrhea, were the most frequent and the most serious. They were of particular importance because of the large proportion of those with diarrhea who had staphylococcal infections which apparently aggra-

vated the enteric symptoms. The numbers of patients with diarrhea listed in table 5 as having predominantly staphylococci in their stools represent only those in whom cultures of the stools were made. However, such cultures were made in less than one-half of the patients who had diarrhea, and some of these cultures were made either early in the course of the diarrhea or some time after the terramycin had been discontinued.

The frequency with which nitrogen retention occurred was not determined because repeated blood specimens were not tested in most of these patients. The four patients in whom nitrogen retention was demonstrated all had severe vomiting and/or diarrhea; two of them died with clinical evidence of uremia, and in the other two the level of non-protein-nitrogen in the blood dropped rapidly after the terramycin was stopped. Although the antibiotic was discontinued or the dosage reduced because of symptoms of toxicity in 20 per cent of the patients, there were a number of additional patients in whom treatment was continued despite severe gastrointestinal symptoms because of the persistence of the infection toward which the treatment was directed.

Fatal Cases

Fatalities are becoming quite infrequent among patients with pneumonia who are treated with currently available antibiotics, and they are not expected to occur among patients who are adequately treated for infections with susceptible organisms, except where treatment is too long delayed or there are unusual extenuating circumstances. It is of interest, therefore, to present briefly the relevant features of each of the seven patients with pneumonia who were treated with terramycin and died.

Case 53. This was a small, emaciated, 89 year old man whose illness began with a cough productive of copious amounts of purulent sputum and accompanied by left pleuritic pain. On the fourth day, when he was admitted to the hospital, he was disoriented, dyspneic with grunting respirations, and slightly cyanotic. His trachea was slightly deviated to the right and there were coarse râles in the bases of both lungs, more on the right side, where there was also moderate dullness. He was promptly started on oral terramycin, 0.5 gm. every six hours. On the following day the temperature dropped from 103° to 99° F., the pulse from 100 to 60, and the respirations from 25 to 20 per minute. However, he remained disoriented and became incontinent, passing frequent loose stools. The stools increased in frequency and became watery. The diarrhea persisted during three days while the drug was omitted. When the temperature again rose and the condition of the patient began to deteriorate progressively, the terramycin administration was resumed in spite of severe vomiting and diarrhea. The signs in the left lung increased, although there were fewer râles at the right base. Other relevant features of the course and laboratory findings are shown in the middle panel of figure 4. The stools obtained before death contained blood and yielded staphylococci in pure culture. Pneumococci were also replaced in the sputum by *Staphylococcus aureus* during the course of therapy.

Case 61. A 73 year old man with a history of chronic cough entered the hospital after four days of illness characterized by weakness, malaise, fever, dyspnea and an increase in cough which soon became productive of thick mucopurulent sputum. He appeared only moderately ill and had signs in the lungs of diffuse bronchitis and

of consolidation of the right lower lobe. The temperature was 101.5° F., pulse 110 and respirations 60. The leukocyte count was 26,100 and the sputum contained type 8 pneumococci in large numbers, but the blood culture yielded no growth. Treatment with oral terramycin was begun promptly with an initial dose of 1 gm., followed by 0.5 gm. every four hours. Within 36 hours the temperature fell to 98° F. and respirations to 35, but the pulse remained rapid. During the next four days the patient remained afebrile and showed gradual but steady improvement, and the leukocyte count dropped to 12,900. Type 8 pneumococci were identified again in the sputum on the day after terramycin was started but not in subsequent specimens, which yielded pure cultures of hemolytic *Staphylococcus aureus*. On the fourth day the patient began to have diarrhea, which increased in intensity and could not be controlled by repeated doses of bismuth and paregoric. The dose of terramycin was then reduced to 0.5 gm. every six hours. The patient later began to vomit all ingested fluids. He became weak and disoriented in spite of vigorous efforts to combat dehydration. His temperature began to rise on the seventh day. The signs of consolidation in the right lung persisted, and coarse râles appeared and increased throughout the rest of both lungs until the patient died on the eighth day, after having received a total of 14.5 gm. of terramycin.

Case 67. This patient had been treated in this hospital three times during the previous two years for hypertensive heart disease with congestive failure, from which he improved each time with rest and digitalis. He also had a chronic cough which increased in severity five days before this admission, when he began to have chills, fever, sweats, severe dyspnea and left pleuritic pain. His sputum, which had been purulent, became blood-tinged and later grossly bloody. He soon became delirious and remained so until he was brought to the hospital. At that time he was severely ill and disoriented, and had signs of consolidation of the left lower lobe and loud rhonchi throughout most of the rest of his lungs. His blood pressure was 130 mm. Hg systolic and 110 mm. diastolic. Treatment with digitalis and intravenous terramycin was started promptly. The course and other relevant findings are depicted in the right panel of figure 4. Signs of pleural effusion were soon made out, and a thoracentesis yielded serosanguineous fluid containing 125 leukocytes, most of them polymorphonuclears, and about 800 erythrocytes per cu. mm. The temperature declined gradually but the patient failed to improve. On the fifth day, when he developed severe watery diarrhea, he rapidly became stuporous and then comatose; his blood pressure dropped steadily and he died on the following day. On the day of death *Staphylococcus aureus* was obtained in pure culture from blood, sputum and the watery feces.

Case 73. A 76 year old woman who had been "in failing health" for 10 years allegedly had a shaking chill two and one-half weeks prior to entry but had been up and around without other symptoms until two days before she was brought to the hospital. At that time she became dyspneic and began to cough and raise rusty sputum. She was emaciated and appeared acutely but not severely ill and had labored noisy respirations. Her lungs were emphysematous, with diffuse rhonchi and musical râles bilaterally. Roentgenograms showed increased bronchial markings. A culture of brownish purulent sputum yielded predominantly type 17 pneumococci and a few colonies of *Staphylococcus aureus*, but the latter organism was also grown from the blood culture. The leukocyte count was 11,000, with 95 per cent polymorphonuclear cells. Treatment with oral terramycin was started promptly, with a dose of 1 gm. followed by 0.5 gm. every four hours. On the following morning the temperature dropped from 100° to 98° F. and the pulse from 115 to 100. A second sputum sample taken after two days of therapy yielded a pure culture of *Staphylococcus aureus*, and no pneumococci could be identified either directly or in the cultures. The patient improved slightly over the following two days and her

pulse dropped to 90. At that time, however, she became disoriented and confused and had signs of consolidation throughout the right lung. During a period of delirium she fell out of bed and sustained a fracture of the ileum. Thereafter she again had a low grade fever, her respirations became labored and she became increasingly cyanotic and died. She had received a total of 12.5 gm. of terramycin in 96 hours without any observed toxic effects. Autopsy revealed inactive rheumatic mitral endocarditis, marked pulmonary emphysema, evidence of aspirated material in the bronchi, and only a minor residuum of pulmonary infiltration. Cultures of cardiac blood and of the lower lobe of each lung yielded no growth.

Case 76. A 60 year old chronic alcoholic was admitted to the hospital in critical condition. He had had an exacerbation of a chronic cough during the previous two and one-half weeks, with a feeling of increasing tightness across his chest. Three days previously he had had a shaking chill and had become very weak, and two days later he again had chills, now accompanied by vomiting and severe pleuritic pain on the left side. He was sweating profusely and was markedly cyanotic and tachypneic. His temperature was 102.5° F., pulse 120, respirations 36 and blood pressure 72 mm. Hg systolic and 44 mm. diastolic. There were signs of frank consolidation, with many râles over the left lower lobe. The white blood count was 4,200, with 44 per cent polymorphonuclear neutrophils. Type 3 pneumococci were identified in great abundance directly in a Neufeld preparation of the sputum, and the blood culture also yielded the same organism. The patient was given oxygen and stimulants, and a slow intravenous infusion of a liter of physiologic salt solution containing 1.0 gm. of terramycin hydrochloride was started quite promptly. The patient, however, rapidly became unresponsive, his pulse became more thready and he died within two hours after the infusion was started and before it had entirely run in. At autopsy, the left lower lobe was densely consolidated and there were 300 c.c. of seropurulent fluid in the pleural cavity on the same side. Cultures of the cardiac blood yielded no growth, but type 3 pneumococci were grown in abundance from the consolidated lobe, from the pleural fluid and from cloudy bladder urine. *E. coli* were also obtained from this urine.

Case 88. A 49 year old woman with a history of hypertension and repeated episodes of asthma and cardiac failure was brought to the hospital because of chills, cough, left pleuritic pain and blood streaked sputum of five days' duration. She appeared acutely and severely ill, with signs of consolidation of the left lower lobe. The temperature was 100° F., the pulse was rapid and thready and the respirations were rapid and shallow. The white blood count was 19,500, with 94 per cent polymorphonuclears. Cultures of a blood-tinged sputum yielded predominantly type 23 pneumococci and many colonies of *H. influenzae*. The blood culture was sterile. Treatment with terramycin was started promptly, with two intravenous doses of 0.5 gm. 12 hours apart and then oral doses of 1 gm. followed by 0.5 gm. every four hours. There was only slight temporary improvement during the first 24 hours, after which the patient became increasingly dyspneic and cyanotic. On the second day the patient began to vomit frequently. A second specimen of sputum obtained on the third day of treatment yielded predominantly *Staphylococcus aureus*. The patient's condition deteriorated progressively as she became increasingly dyspneic and cyanotic and then stuporous and finally comatose. The nonprotein-nitrogen in the blood taken on the day before she died was 127 mg. per 100 ml. The patient died after receiving a total of 1 gm. of terramycin intravenously and 9.5 gm. by mouth over a period of three and one-half days. Autopsy revealed an enlarged heart, diffuse hemorrhagic pneumonia involving mostly the right middle and left lower lobes, and a chronic pyelonephritis. Cultures of the spleen and of two areas of hemorrhagic consolidation in the lungs yielded abundant growths of *Staphylococcus aureus*. Because of the gross character of the pulmonary lesion, and because this patient was

admitted during the 1951 influenza epidemic, some of the hemorrhagic lung tissue was used in attempts to isolate influenza virus by repeated amniotic inoculation and passages in embryonated hen's eggs. No virus was recovered.

Case 83. This was the only fatal case not included among the pneumococcal pneumonias. The patient was a 55 year old woman who entered the hospital after having vague malaise and muscular aches for five days, and headache, backache, chills, fever, sweats and cough productive of scanty mucoid sputum for two days. She had received penicillin for two days and two doses of chloramphenicol before she was sent to the hospital. Her temperature was 105° F., pulse 110, respirations 25 and blood pressure 190 mm. Hg systolic and 90 mm. diastolic. The only positive finding on physical examination was scattered râles in both lungs posteriorly; roentgenograms showed finely mottled densities but no gross consolidation. A culture of blood-streaked sputum yielded only *Streptococcus viridans*, and the blood culture showed no growth. The white blood count was 11,600, with 88 per cent polymorphonuclears. The blood urea nitrogen was 12 mg. per 100 ml. Urinalysis was entirely normal except for a low specific gravity, and a culture of the urine was sterile. Treatment was started promptly, with 300,000 units of penicillin intramuscularly every three hours. On the following day there were signs of consolidation of the lower lobe and more râles appeared in both lungs. The patient's temperature remained elevated and her general condition grew worse, the blood pressure falling to 90/40. She was given intravenous fluids and adrenal cortical extract intravenously and subcutaneously, and was started on oral terramycin, 1 gm. followed by 0.5 gm. every four hours. On the day after this treatment was started, the temperature dropped to about 102° F., where it hovered for four days and then gradually fell to normal over another four-day period. The pulse, however, remained rapid and thready, and the patient became disoriented and unresponsive and developed a slurred speech. Lumbar puncture yielded normal spinal fluid. On the second day of terramycin therapy the patient began to vomit, and shortly thereafter she developed diarrhea which increased in severity and persisted. Cultures of the watery stools when the diarrhea started revealed a normal fecal flora, but Monilia predominated in subsequent cultures. On the fourth day, because of urinary incontinence, a retention catheter was placed in the bladder. The urine was normal and a culture showed no growth at this time. Subsequently, however, the urine became increasingly cloudy, and cultures were overgrown by *B. proteus*. On the sixth day the bladder urine, though odorless, had a fecal character both grossly and microscopically, indicating that she had developed a rectovesical fistula. The patient's condition then deteriorated steadily. She finally became uremic and acidotic and died on the eleventh hospital day. She had received a total of 25 gm. of terramycin in nine days.

From these case summaries it is seen that among the seven fatal cases there was only one patient (case 76) so critically ill at the time of admission that there was no adequate opportunity to evaluate the effect of terramycin on the pneumonia. This patient died while receiving his initial dose of terramycin, and the possibility must be considered that a reaction to the intravenously injected antibiotic may have hastened the fatal outcome. Nevertheless, some antipneumococcal action of the terramycin is attested in this case by the failure to grow organisms from the cardiac blood post mortem after only the single dose of antibiotic, although the blood culture taken just before that dose was started yielded pneumococci.

There was one additional patient, case 73, in whom the rôle of the terramycin in the fatal outcome is difficult to evaluate. The potent antibacterial

property of the terramycin is attested in this case, also, by the fact that the pneumococci, which were present in abundance before terramycin was started, could not be demonstrated subsequently, and the staphylococcus that was cultured from the blood at the time of admission and was later found in abundance in cultures of the sputum could not be recovered from the cardiac blood or the lungs at autopsy. This patient was the only one among those who died who did not have serious gastrointestinal symptoms from ingestion of the antibiotic. The fracture sustained by this patient during an episode of delirium undoubtedly contributed to the fatal outcome in this case.

Case 83 also is a complicated one, in which the exact nature and course of events, and particularly the rôle of the pulmonary infection, are not clear. In this patient, however, the severe vomiting and diarrhea which resulted from ingestion of terramycin were followed by evidence of a rectovesical fistula and uremia, in spite of the fact that the patient had normal urinary findings during the first few days of the treatment and had had no gastrointestinal complaints before the terramycin was started.

In the remaining four patients there were severe superinfections with *Staphylococcus aureus* which undoubtedly were responsible for, or at least contributed seriously to, the fatal outcome. These staphylococcal infections probably involved the lungs in each instance, as evidenced by persistence and spread of the pulmonary lesions and by the complete replacement of the usual organisms of the sputum by large numbers of staphylococci. The staphylococcal infection of the lung was confirmed by the autopsy findings in case 88.

Severe gastrointestinal symptoms from the terramycin ingestion also featured prominently in each of these four cases. These gastrointestinal symptoms were accompanied by staphylococcal infection of the bowel in three of these patients, as evidenced by the intense watery diarrhea and by the essentially complete replacement of the fecal flora by staphylococci. In the fourth patient there was marked nitrogen retention resulting from the severe vomiting.

Discussion

The data presented offer convincing evidence of the effectiveness of terramycin against the most important of the bacteria which may cause pneumonia, namely, the pneumococcus. There is also evidence of its effectiveness against the hemolytic streptococcus and, to a lesser degree, against *H. influenzae*. Clinically there was also suggestive evidence of the effectiveness of terramycin in primary atypical pneumonia, based only on the effects in four cases that were available for treatment.

The potent antipneumococcal effect was manifested in the cases of pneumococcal pneumonia by the prompt disappearance of pneumococci from the blood of bacteremic cases and their rapid elimination from the sputum in almost all cases after terramycin therapy was started. It was also evi-

denced by the failure to demonstrate pneumococci in pleural fluids obtained after one or more days of terramycin therapy. In vitro, all of the pneumococci tested were found to be moderately or highly sensitive to terramycin. This antipneumococcal effect of the antibiotic was reflected clinically by the regularity with which the fever declined and symptoms referable to the acute pneumococcal infection began to improve within the first 24 to 48 hours after terramycin was started.

The outstanding and probably the most important features of the present cases, however, are the frequency and rapidity with which pathogenic strains of *Staphylococcus aureus*, almost all of them highly resistant to terramycin, emerged and replaced the flora of the sputum during treatment with this antibiotic. The purulent character of the sputum, the persistence of staphylococci in such sputum for unusually long periods after the apparent subsidence of the pneumococci or other primary infections, the recurrence and persistence of leukocytosis and the relatively long time during which it was still possible to demonstrate signs of pulmonary infiltrations in a significant proportion of the cases during and after the terramycin therapy, suggest very strongly that the staphylococci played an important pathogenic rôle in maintaining the infection in the lung. They also indicate quite clearly that terramycin was not only ineffective in clearing these staphylococcal infections but may even have played a significant part in sustaining or aggravating them, at least in some of the cases. No attempt was made to determine the presence of terramycin-dependent strains.

The frequent tendency of terramycin to produce gastrointestinal irritation in the present cases and the association of the terramycin-induced diarrheas with massive numbers of pathogenic staphylococci are further evidence not only of the significance of staphylococci in the present cases but also of the probable importance of the terramycin therapy in initiating and sustaining the infections with these organisms. These staphylococcal infections of the gastrointestinal tract, occurring as they did in seriously ill patients, resulted in deterioration of the condition of many of the patients at a time when their primary pulmonary infections were apparently being eliminated. The evidence suggests very strongly that these gastrointestinal infections prolonged significantly the period of morbidity of many of the patients who recovered, and played an important rôle in the failure of some of the patients to survive. These untoward results of terramycin therapy have not been limited to patients with pneumonia,[15, 16] nor have these serious effects been confined entirely to therapy with terramycin.[16]

Comparisons of the results that have been presented here with those reported by others are difficult to make and are not justified. It is for that reason that the data have been presented in such detail. It is possible that the doses used were greater and the duration of treatment longer than those necessary to produce the desired clinical and bacteriologic effects with a minimum of toxicity or of complicating superinfections. The unfavorable

features of the present cases may also have been due, in part, to the generally advanced age of so many of the patients and to the large proportion of them who had underlying complications. Another important factor may have been the increasing frequency with which staphylococci are being encountered as important secondary invaders among patients in this hospital who are under treatment for all types of infections. It may also be, in part, a consequence of the widespread use of penicillin and other antibiotics for prophylaxis and for many minor indications.[17, 18]

The frequency with which staphylococci were identified in the stools in the present study was dependent, in large measure, on the fact that in this laboratory cultures on blood agar plates are included in the bacteriologic studies of feces. The media ordinarily used for the culture of stools are designed to aid in the isolation and identification of gram-negative enteric pathogens and inhibit the growth of gram-positive cocci.

Comparisons of the results obtained with terramycin in the present series with those obtained in similar cases in other clinics by the use of other antibiotics are certainly not warranted. In this clinic, however, comparable cases under treatment with aureomycin were studied in a very similar manner during the preceding season. Both the clinical and bacteriologic results appeared to be more favorable, the toxic effects were less serious, and staphylococcal infections did not play an important rôle in the aureomycin-treated cases. This may possibly be attributable, in part, to the increasing prevalence of antibiotic resistant strains of staphylococci in this hospital during the interim.[18] Unfortunately, there was no parallel series of cases treated with aureomycin during the same season.

Summary and Conclusions

Clinical and bacteriologic findings in 91 patients with pneumonia who were treated with terramycin have been presented. The bacteriologic results and the immediate clinical effects indicated that terramycin was highly effective against pneumococcal pneumonia. In most of the other pneumonias in which a bacterial etiology was proved or suspected, and in the four cases of primary atypical pneumonia, the immediate effects of terramycin therapy were also favorable.

Replacement of the flora of the sputum by staphylococci, slow clearing of the lungs, and recurrence or persistence of leukocytosis indicated that the beneficial effects of terramycin were, in part, vitiated in many of these patients by superinfections with the staphylococcus.

Gastrointestinal symptoms from terramycin were frequent and in many patients were quite severe. In many of the patients with terramycin-induced diarrhea, the fecal flora was replaced by pathogenic staphylococci. These staphylococcal infections of the intestinal tract added considerably to the morbidity of many of the patients who recovered.

Seven of the patients died. In five of these seven patients the toxic

effects of terramycin on the gastrointestinal tract may have contributed in large measure to the fatal outcome. In addition, staphylococci played an important pathogenic rôle in the lungs of four of these patients.

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CURRENT CONCEPTS OF BERYLLIUM POISONING*

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The first major reports of industrial hazards and diseases were made about 40 years ago. It was soon realized that the field would become a large one and that unusual causes and lesions necessarily would be discovered. Beryllium poisoning is one of the newer occupational diseases. It is of particular interest to internists because of its multiple manifestations. There is much to suggest that it is of systemic involvement rather than a source productive of only dermal and pulmonary lesions. It is a condition which should stimulate the internist to further coöperation with medicine in industry.

Our experience with the beryllium problem in Northeastern Ohio was initiated from observations of workers employed in plants which extracted beryllium and its compounds from the ore, and dated from the death of one such worker in the latter part of 1940. My own interests and observations from that date have been carried out in conjunction with Dr. J. M. DeNardi, Dr. M. G. Carmody and Dr. C. R. Hughes. In the past 10 years we have had the opportunity of observing all of the clinical manifestations of beryllium poisoning, not only in workers employed in the basic beryllium industry but from multiple other sources. More than 450 patients manifesting one or more phases of the problem have been observed and studied. Our initial report was made in 1943,[1] and subsequent additional observations [2, 3, 4, 5, 6] have been related by us in the literature. As mentioned in our first article, we discovered that German, Italian and Russian physicians had reported on similar diseases occurring in workers exposed to certain beryllium compounds between the years 1933 and 1936.[7, 8, 9]

At about the same time that our attention was directed to the problem in Northeastern Ohio, or shortly thereafter, Hardy and Tabershaw detected the chronic form of the disease in Massachusetts and summarized their observations in a conclusive report in 1946.[10]

It is difficult in this presentation to do justice to all who have worked and experimented on the beryllium problem. Within only a few years several hundred contributions on the subject have appeared in the medical literature. Until his untimely death a few years ago, the help of Dr. LeRoy Gardner of Saranac had been enlisted in all of our own observations. Dr. Gardner carried out intensive investigations. Splendid clinical and laboratory research has been reported from multiple points in this country, England and elsewhere. In addition to the investigations being continued by Vor-

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From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

wald and his colleagues at Saranac Lake, excellent supplementary work is being done by DuBois et al. at the University of Chicago, Howland et al. at Rochester University, Dutra et al. at Kettering Laboratory of the University of Cincinnati, and many other investigators. As in many of the better known occupational diseases, there is much to be learned of the mechanism of beryllium poisoning. Before proceeding, however, it may prove desirable to review briefly the metallurgy and usage of beryllium and its clinical manifestations.

Beryllium is a metallic element which was first recognized more than 150 years ago. Its atomic weight is 9.02 and its position in the atomic weight chart is number 4. It is considered a rare element, on the basis that minerals containing beryllium have not been found in large compact deposits. Only in the past two or three decades has a sufficient amount been obtained for metallurgic extraction. The first attempts at processing it from the ore in this country began in 1931. Its use in fluorescent lamps began in 1938. The ore beryl, which is essentially a beryllium silicate, yields approximately 12 per cent beryllium oxide, or about 4 per cent of beryllium metal. Due to the unusual properties of beryllium and its compounds, it has often been called the "glamour child" of metallurgy. Beryllium metal is lighter than aluminum, extremely penetrable to roentgen-ray, a remarkable transmitter of sound and an excellent source of neutrons. Examples of its uses are the "window" for roentgen-ray tubes and nuclear physics developments. Beryllium oxide has a melting point of 2,570 degrees C., is an excellent insulator at high temperatures, has unusual resistance to thermal shock, and has high thermal conductivity. Examples of the uses of beryllium oxide include high temperature crucibles, its previous use in the phosphor of fluorescent lights (and the continued use in the phosphor in neon tubing), and cathode heating elements in radio tubes, and in ceramics. The addition of only a small amount to copper produces an alloy recognized for its unusual resistance to fatigue and impact, its corrosion resistance, freedom from elastic drift, and high electrical and thermal properties of conductivity. Beryllium copper alloy has multiple uses, therefore, such as specialized spring parts and safety tools. From this brief summary one can see that beryllium has played an essential part in multiple industries and still has great industrial potentialities.

Machle et al.[11] have ably expressed the definition of beryllium poisoning as "a general disease characterized clinically by pulmonary insufficiency and having the major pathological changes in the lungs." The presenting complaints of beryllium workers or others exposed to beryllium compounds have consisted of acute or chronic dermal lesions and/or acute or chronic respiratory symptoms. The most common manifestation of employees in the basic beryllium industry is the acute eczematous contact type of dermatitis shown in figure 1. This generally appears in hypersensitive individuals between the seventh and fourteenth days after exposure, and disappears within a few days to a week after removal from contact. It has been found

a useful yardstick in terminating employment, and a preventive of possible serious difficulty. A number of workers in the basic extraction plants also have developed ulcers, usually over a knuckle, apparently the result of an implantation of a beryllium compound at the site of an antecedent abrasion. An example is shown in figure 2. These have been prone to become indolent unless prevented by simple curettage or local excision. The chronic beryllium granuloma which may develop at the site of a laceration occasioned by a broken fluorescent lamp tube (in which the phosphor contained beryllium oxide) is shown in figure 3. In our experience, these are purely

FIG. 1. Photograph of the acute eczematous contact type of dermatitis occurring in workers employed in extracting beryllium from the ore.

local lesions which may be cured by adequate excision. The pathology of the chronic beryllium granuloma, as shown in figure 4, is identical to that seen in the chronic pulmonary form of the disease, showing a sarcoid-like granulomatous reaction.

The so-called *acute* respiratory beryllium involvement may consist of varying degrees of minor upper respiratory tract symptoms or of a demonstrable pulmonary lesion. The latter has been called acute berylliosis or acute pneumonitis in a beryllium worker. We have observed 98 cases of pneumonitis in which 12 fatalities occurred. The roentgen-ray change has invariably followed the onset of a relatively nonproductive cough and pro-

gressive dyspnea by two or three weeks on the average. The 12 casualties from this form of beryllium poisoning occurred between the twenty-fifth and thirtieth days. In the non-fatal acute cases the total duration of the illness up to complete clinical and roentgen recovery has not exceeded four months. The follow-up on the majority of the recovered patients (in several instances a 10 year review) has, in our experience, so far shown no evidence of difficulty, and particularly no evidence of the chronic form of the disease. As shown in figures 5 and 6, the roentgen-ray pattern demonstrates a symmetrical infiltration. As shown in figures 7 and 8, the pathology of the acute disease is essentially an intra-alveolar edematous exudate, the predominant cell of which is mononuclear; death is the result of asphyxia, with or without acute cor pulmonale. The clinical and laboratory studies on these patients have shown a striking absence of infectious etiology and, when tested appropriately, have demonstrated during the acute illness a decrease in liver function. Hyperglobulinemia has been found consistently (figure 11).

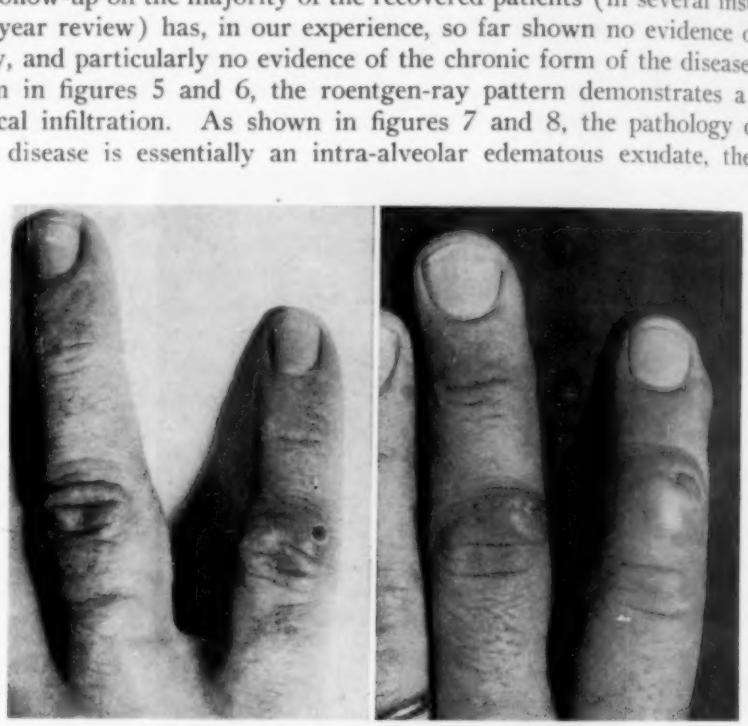

FIG. 2. (*Left*) Photograph of the so-called acute "beryllium ulcer," which is felt to be the result of an implantation of a beryllium compound at the site of an antecedent abrasion, occurring in workers in the basic extraction plants.

FIG. 3. (*Right*) The chronic beryllium skin granuloma which may develop at the site of a laceration occasioned by a broken fluorescent lamp tube (in which the phosphor contained beryllium oxide).

Chronic lung injury due to beryllium poisoning has been termed "chronic berylliosis" and "chronic pulmonary granulomatosis." This form of the disease has displayed a number of unique features. The onset of symptoms following exposure has been delayed as long as 10 years. In contrast to the acute form of the disease, the roentgen-ray changes in a num-

ber of instances have been evident prior to the onset of symptoms, or at least prior to the absence of noticeable ill health. As in the acute form, the symptoms have been cough, shortness of breath, anorexia and weight loss, although of less rapid progression. A small percentage of the patients experiencing the chronic form have had bouts of fever. Symptoms in women have often followed the beginning of pregnancy or delivery. A higher mortality rate exists in the chronic cases, as one-third in our series have already died; of the remaining two-thirds, one-third have shown progressive deterioration, with the exception of those patients accepting ACTH therapy. Examples of the roentgen-ray change in the chronic form of the disease are shown in figures 10 and 11, which demonstrate the basic disseminated fine nodular infiltration. The next figure (figure 12) shows that the histopathology is that of a chronic sarcoid-like granulomatous response. In

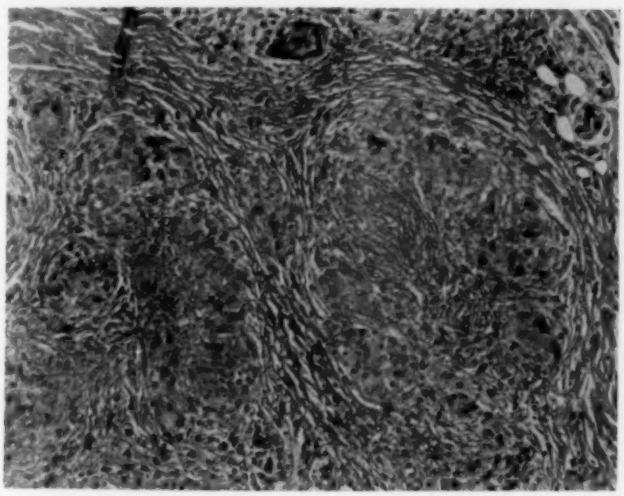

FIG. 4. Photomicrograph showing the typical sarcoid-like granulomatous reaction in the chronic beryllium skin granuloma shown in figure 3.

contrast to the pathology in the acute form of the disease, the lesions are predominantly interstitial, chronic and granulomatous. The right myocardium is hypertrophied, and death is due to chronic cor pulmonale.

As Machle [11] has stated, the essentials for the diagnosis of beryllium poisoning include a significant history of exposure, occupational or otherwise, a characteristic clinical pattern with consistent laboratory and roentgen-ray observations, and the finding of beryllium in tissues or urine. Hardy [12] bases her conclusion that beryllium poisoning is a systemic disease on her observation of renal calculi in one-fifth of her cases and on the frequent finding of hypercalcuria, negative nitrogen balance, reduced liver function, hyperglobulinemia, and disturbances of the blood calcium, blood phosphorus and alkaline phosphatase.

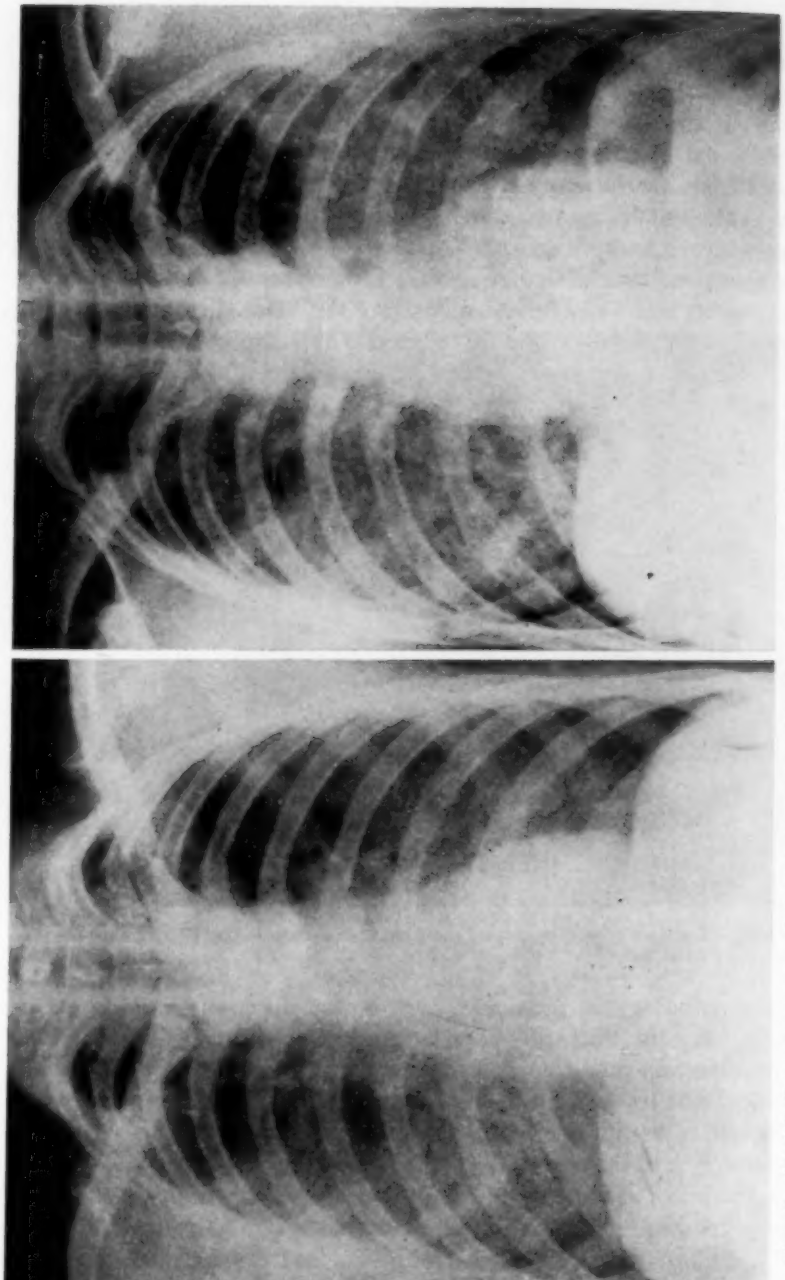

FIG. 5. (*Left*) Roentgenogram of the acute pneumonitis in a beryllium worker (acute pulmonary berylliosis) showing the symmetrical diffuse infiltration. This x-ray was made one week after onset of symptoms (and two weeks after exposure) in an 18-year-old boy.

FIG. 6. (*Right*) Roentgenogram of the same patient as shown in figure 5, nine days later. The further progression of the involvement is noted. The patient died eight days after this x-ray examination with the postmortem study confirming the diagnosis.

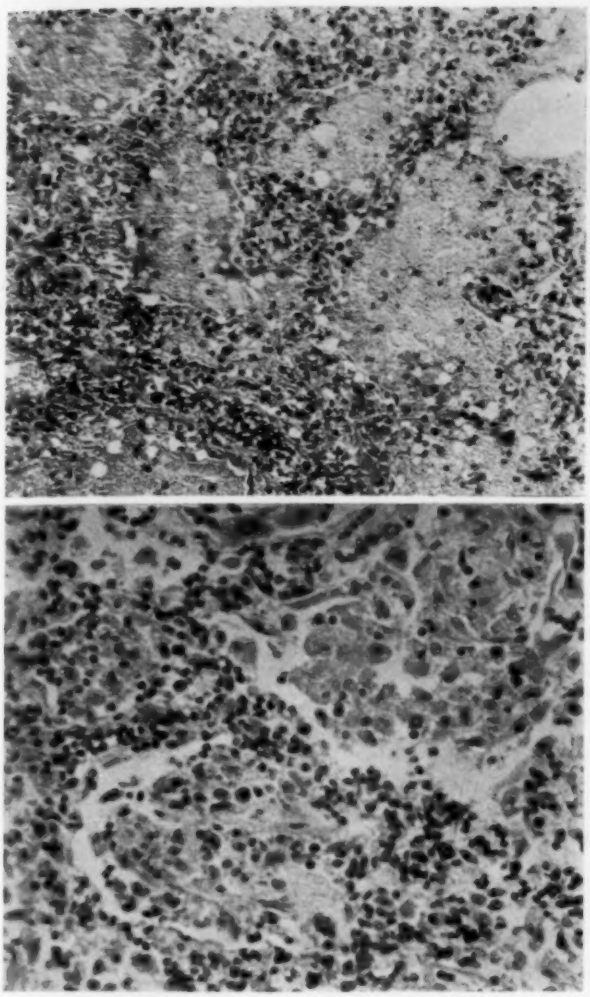

FIG. 7. (*Above*) Photomicrograph of the lung pathology in the acute pneumonitis of beryllium poisoning (acute pulmonary berylliosis). In this instance the patient died on the twenty-first day after onset of symptoms and the picture is predominately an acute one with marked intra-alveolar edema. In acute pulmonary berylliosis the lungs are heavy and uniformly firm or liver-like. The pleura is purplish to brownish red and smooth. On section the pulmonary tissue bulges slightly, is coarsely lobulated or smooth surfaced, non-crepitant and tannish-red to pinkish-gray with occasional purplish-red patches. A slight or moderate amount of thin fluid can be expressed. The bronchi may contain thin froth. The majority of alveoli contain exudate or cells variably, as follows: (1) pink staining coagulum distending alveoli and including mononuclear phagocytes and lymphocytes; (2) masses of mononuclear phagocytes with variable vacuolation; (3) plugs of fibroblasts filling or partly filling alveoli and infiltrated by lymphocytes and plasma cells; (4) fibrinoid material, at times irregularly lining alveoli. Alveolar lining cells may be swollen or desquamated. Rare scattered alveoli are free of exudate. Terminal bronchioles occasionally are interrupted by the fibroblastic masses and may show squamous metaplasia. The alveolar walls and septa are infiltrated in patches by plasma cells and lymphocytes and may also be thickened by fibroblastic hyperplasia. A recent infarct is rarely present. The lesions are predominately intra-alveolar and acute or subacute. Death is due to asphyxia with or without acute cor pulmonale.

FIG. 8. (*Below*) Histopathology of higher magnification in a patient with acute pulmonary berylliosis, who died on the thirty-fifth day of his illness. As noted, the pathology is less acute than shown in the case in figure 7.

In the acute form of the disease, central necrosis of the liver has been found in addition to the pulmonary lesion (figure 13). In the chronic form observed at autopsy, beryllium has been recovered from renal calculi and from cervical and axillary lymph nodes, as well as from the liver (figure 14).

To us, the first indications of beryllium poisoning were the presence of skin lesions and the recurrence of acute pneumonitis in affected workers who returned to the same employment. The medical hazard from beryllium has been reported as having occurred throughout its use, except in the fields of mining, handling and shipping as related to the ore beryl. Beryllium metal

CLEVELAND CLINIC

PLASMA PROTEINS

Tiselius Method

Name _____ No. 534-287 Date Jan. 12,1948

Total plasma proteins 6.51 gm./100 ml.	Method Pregl-Kjeldahl
(Normal average 6.51, range 5.94-7.82 gm.)	
Albumin 2.18 gm./100 ml.	33.5 % of total proteins
(Normal average 4.09, range 3.72-5.11 gm.)	(Normal average 62.7, range 60.1-67.2%)
α globulin 1.14 gm./100 ml.	17.5 % of total proteins
(Normal average 0.47, range 0.38-0.66 gm.)	(Normal average 7.2, range 6.0-8.7%)
β globulin 1.03 gm./100 ml.	15.8 % of total proteins
(Normal average 0.81, range 0.65-1.07 gm.)	(Normal average 13.1, range 11.0-15.9%)
γ globulin 1.09 gm./100 ml.	16.7 % of total proteins
(Normal average 0.77, range 0.60-0.91 gm.)	(Normal average 11.7, range 8.6-14.8%)
Fibrinogen 1.07 gm./100 ml.	16.5 % of total proteins
(Normal average 0.33, range 0.16-0.48 gm.)	(Normal average 5.4, range 2.8-7.2%)

FIG. 9. Photograph of the Tiselius pattern showing the relative hyperglobulinemia which has been found to be consistently present in the acute beryllium lung problem. It is also present, although to a lesser degree, in the chronic beryllium lung disease.

(particularly in its machining) and beryllium compounds have been the cause of the clinical disease. The soluble salts of the compound appear to have been the chief cause of the acute disease. Environmental studies by Eisenbud et al.[13] have incriminated most of the beryllium compounds, including beryllium metal dust, dust and mist of beryllium sulfate, dust and fumes of beryllium fluoride, and dust and fumes of beryllium oxide. They have shown that the acute disease can be caused by a single exposure of only a few minutes' duration to either beryllium fluoride or beryllium sulfate. The exact safety level of exposure has not as yet been established completely. It appears significant that few cases of beryllium poisoning oc-

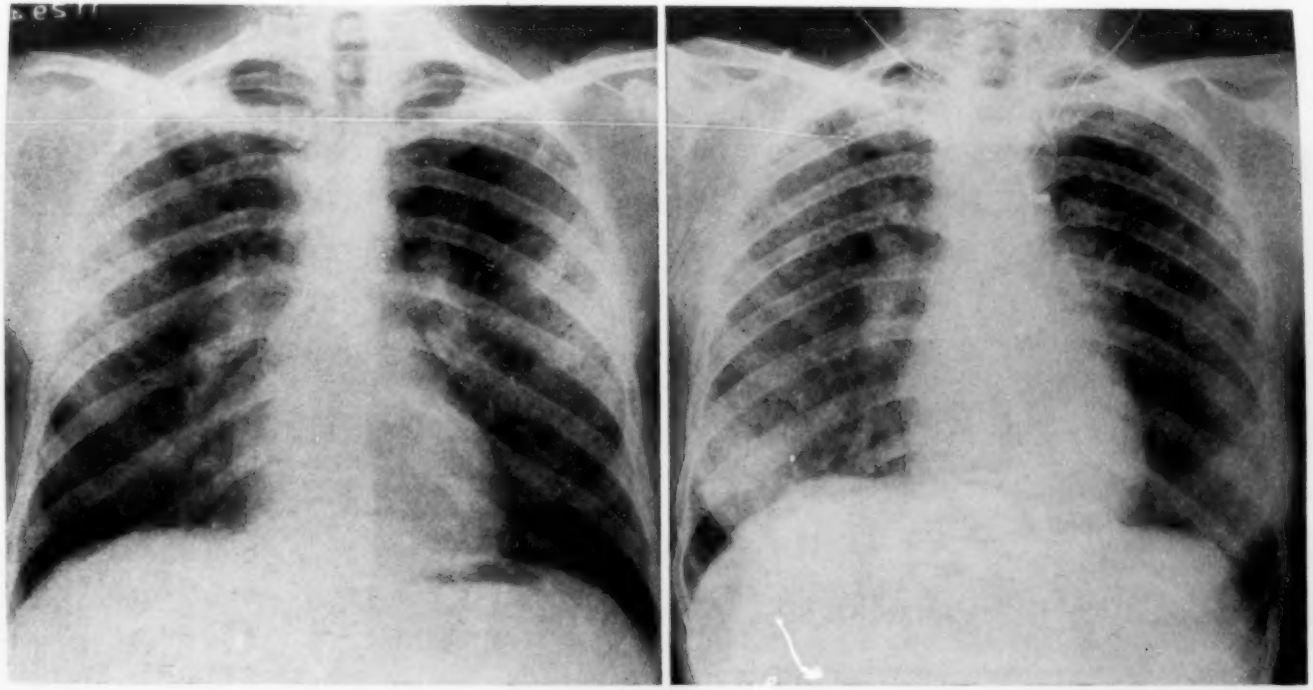

FIG. 10. (*Left*) Chest roentgenogram in chronic beryllium poisoning (chronic pulmonary berylliosis). Fine generalized nodulation is observed. The patient, age 36, had experienced symptoms of a progressive, relatively non-productive cough, anorexia and 20 pound weight loss for one year at the time of this x-ray examination, following a latency period of four years from time of exposure.

FIG. 11. (*Right*) Roentgenogram of chest with a similar history to the patient's x-ray shown in figure 10, showing slightly more extensive involvement with chronic granulomatosis in a beryllium worker (chronic pulmonary berylliosis).

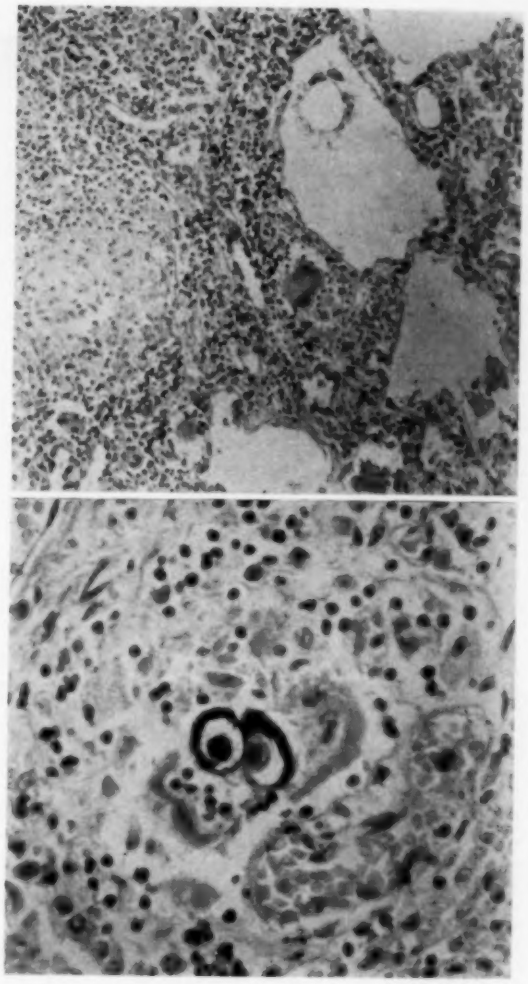

FIG. 12. (*Above*) Photomicrograph of the histopathology in the chronic beryllium lung disease (chronic pulmonary berylliosis), showing the picture of a chronic pulmonary granulomatosis. In chronic beryllium poisoning the lungs are moderately heavy and are irregularly firm and partly crepitant. The pleural surfaces are patchily gray and yellowish gray. On section, the pulmonary tissue is variably non-crepitant, yellowish white and granular, partly crepitant and gray with miliary yellowish foci and are emphysematous. The majority of alveolar walls and septa are thickened, definitely at times by: (1) foci of histiocytes and foreign body giant cells, often of Langhans' type, more loosely arranged than the usual tubercle and with intermingled lymphocytes and occasionally including conchoidal bodies; (2) hyaline, fibrous and fibroblastic proliferation; (3) foci of lymphocytes and plasma cells. The alveoli in patches are noticeably reduced in size or obliterated by the thickening of their walls and are lined by cuboidal and low columnar cells. Intra-alveolar masses of mononuclear phagocytes are present occasionally. In areas the alveoli are emphysematous with thin walls. The hilar and bronchial lymph nodes contain many foci of histiocytes and giant cells. In contrast to the pathology seen in the acute pulmonary berylliosis, the lesions in chronic pulmonary berylliosis are predominately interstitial, chronic and granulomatous. The right myocardium is hypertrophied and death is due to chronic cor pulmonale.

(*Below*) Photomicrograph showing the conchoidal body which is occasionally seen in the chronic beryllium lung.

curred in the manufacture of fluorescent lamps (when beryllium was still being used in the phosphor) where the amount of beryllium oxide employed was 2 per cent or less. It would also seem significant that Machle,[14] in a large survey, found no incidence of the disease where the concentration of

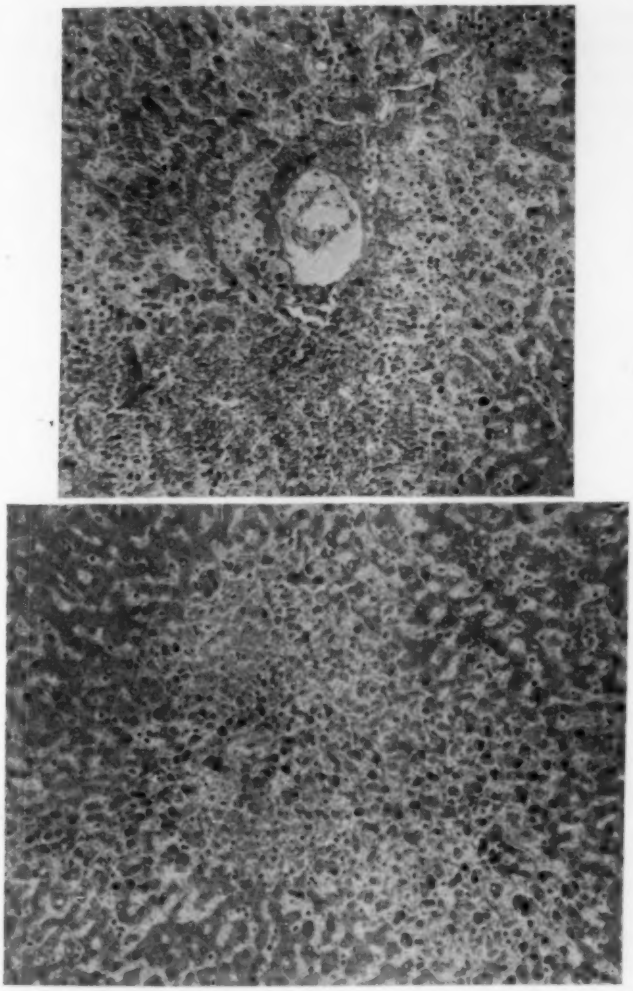

FIG. 13. (*Above*) Photomicrograph of liver in acute beryllium poisoning, showing central necrosis.

FIG. 14. (*Below*) Photomicrograph of the liver in chronic beryllium lung disease, showing granulomatous involvement.

beryllium in the air was 70 micrograms per cubic meter or less. Until the safety levels of beryllium content in the air have been fully determined, arbitrary measures are being maintained. One of the large basic beryllium producing companies has established and met a control level of an average

concentration of beryllium in the air of 2 micrograms per cubic meter (never in excess of 25 micrograms per cubic meter for any appreciable period).

Much research has been carried out on the problem. Toxicity of the beryllium compound has been clearly demonstrated in animals, and many workers [15] have shown lung, liver and renal damage in these studies. The chronic form of the disease from the standpoint of the lung has not been produced completely in animal experimentation as yet. Gardner et al.[16] have been able consistently to produce osteogenic sarcoma from intravenous beryllium compound injections in the rabbit, a condition which has not been

FIG. 15. Photograph of an arm showing positive patch-tests to beryllium compounds (in this instance BeF_2), a consistent finding in beryllium workers having the eczematous contact type of dermatitis. This is believed to indicate, in this form of beryllium poisoning, a hypersensitization phenomenon rather than a primary irritant reaction.

observed in humans. DeNardi [17] has informed me that one of our patients who had recovered from acute berylliosis died recently from bronchogenic carcinoma; this finding would appear to have no clinical significance at present, as it represents no higher incidence of bronchogenic carcinoma among our total cases than in the population as a whole.

Experimental work undertaken at the Berkeley Cyclotron with Be_7,[18]* a radioactive isotope, has shown in tracer experiments on small animals that beryllium enters bone (after exceeding a certain level of tolerance of excre-

* Be_7 was used by the Berkeley Cyclotron and supplied on authorization from the Isotopes Division, U. S. Atomic Energy Commission.

tion) and remains there. We might hypothesize that, in the chronic form of the disease, those who have experienced such retention may have a release of beryllium when undergoing some acute or chronic illness, or from a metabolic strain such as that accompanying pregnancy.

It has been demonstrated clearly by one of my Cleveland Clinic colleagues, Dr. G. H. Curtis,[19] a dermatologist, that the eczematous contact type of dermatitis in beryllium workers is a hypersensitization phenomenon rather than a reaction to a primary irritant. His clinical, histologic and experimental study has confirmed the criteria for the dermatitis as an allergic reaction. Figure 15 shows an example of the positive patch tests to high dilutions of beryllium compounds. Curtis sensitized seven of 16 individuals who had never been exposed to beryllium and who were used as controls. He and others feel that hypersensitivity may also explain the mucous membrane and pulmonary changes in the acute respiratory tract beryllium problem.

Grier,[20] Klemperer [21] and DuBois,[22] working independently, have satisfied themselves that beryllium in vitro and in vivo has an inhibitory effect on the alkaline phosphatase enzymes. Recent publications from Britain [23] add to the suggestion that beryllium displaces magnesium, and that inhibition of enzymes brings about widespread cellular changes, producing subsequent symptoms and signs of the chronic form of the disease.

Although it is evident that much has been accomplished, a great deal remains to be learned of the mechanism of the treatment of beryllium poisoning. Until the use of ACTH or cortisone, nothing of particular value had been discovered in therapy. Oxygen previously had been found most important, but apparently in only a symptomatic way. BAL and multiple other measures had been employed without benefit. Much improvement has been derived recently from ACTH and cortisone medication, and regression has been observed in certain patients having the progressive unrelenting and disabling form of the chronic disease. Although its eventual value remains to be evaluated, it is at present the treatment of choice in the most severe forms of the disease.

It should be emphasized that, as is usually the case, industrial hygiene and safety engineering have significantly reduced the incidence of beryllium poisoning. In my opinion, the excellent control measures being carried out in industry are eliminating it as an important medical problem.

Summary

Beryllium poisoning is one of the newer occupational diseases. There is much to suggest that it causes systemic involvement, rather than merely a pulmonary lesion, its most severe manifestation. It is a condition which should stimulate the internist to further coöperation with industrial medicine.

Beryllium has been called the "glamour child" of metallurgy. The multiple usage of it and its compounds and alloys has been discussed. The

author and his colleagues have had the opportunity of ob ving all of the clinical manifestations of beryllium poisoning since 194(Examples of each are shown, including the clinical and pathologic findir

A summary of the extensive and excellent research w being carried out in various parts of the country and elsewhere is presente It has been demonstrated clearly that the eczematous contact type dermati is in beryllium workers is a hypersensitization phenomenon. There is much to suggest that the acute beryllium lung problem may also be an allergic reaction. Facts and theories have been presented as to the pathogenesis f the chronic granulomatous form of the disease. Independent researcl conducted at three places in this country and one in Great Britain suggests that beryllium has an inhibitory effect on the alkaline phosphatase enzymes. The hypothesis that beryllium may compete for magnesium in magnesium-activated enzymes may provide an explanation of the toxic properties of beryllium, although much remains to be clarified. Expansion of our knowledge of this occupational disease may give basic clues to the body's reactions in the large group of granulomatous diseases.

Multiple treatments have been employed, but no specific antidote has been found. ACTH and cortisone therapy have been encouraging and have produced noticeable symptomatic benefits; they have proved to exert a regressive influence in a number of patients demonstrating the chronic and progressive granulomatous forms of the disease.

A remarkable reduction in the incidence of beryllium poisoning has occurred since the institution of safety engineering and industrial hygiene in the involved industries.

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THE MANAGEMENT OF LUNG ABSCESS, WITH SPECIAL REFERENCE TO THE PLACE OF ANTIBIOTICS IN THERAPY *

By E. H. Drake, M.D., F.A.C.P., *Detroit, Michigan,* and F. Mason Sones, Jr., M.D., *Cleveland, Ohio*

Successful management of the patient with lung abscess demands the coördinated efforts of internist, radiologist, bronchoscopist and thoracic surgeon. The dynamic nature of the underlying pathologic process requires constant reëvaluation of the individual case, rather than single regimented approach. Any reduction in mortality and morbidity must depend on an understanding of the factors necessary for the development of pulmonary necrosis, a familiarity with their earliest clinical manifestations, and an ability to correlate the individual patient's course with the natural history of the disease.

The diagnosis of lung abscess has been made on 108 patients studied in this hospital during the past decade. In 45 of these the diagnosis was not supported by the demonstration of frank cavitation on roentgen-ray or at autopsy. It is believed that many of these represented early abscess formation, in which resolution of the process occurred either spontaneously or by reason of the prompt institution of effective therapy.[8] Five cases in which the diagnosis was positive were observed over an inadequate period of time. Four cases were later demonstrated to have been secondary to malignant growths; four were actually complications of bronchiectasis; one proved to be a basal tuberculous cavity, and in four the diagnosis was an incidental autopsy finding. There remained 45 cases of solitary lung abscess, the diagnosis being supported by definite roentgen-ray or postmortem cavity demonstration. These form the basis for this report.

Of the 45 cases considered suitable for study, there were 36 males and nine females, an incidence of four to one. Age at which symptoms appeared is shown in table 1.

Factors predisposing to the development of lung abscess must be evaluated with respect to their relative importance in the train of events which may lead finally to the destruction of lung parenchyma. Pulmonary necrosis depends on three major factors for its development:

(1) Bronchial obstruction, leading to impairment of alveolar gas exchange, and eventual atelectasis.

(2) Infection distal to the point of obstruction.

(3) Interference with the blood supply to the involved segment of pulmonary tissue.

* Received for publication September 1, 1950.
From the Cardio-Respiratory Division of the Henry Ford Hospital, Detroit, Michigan.

Often the obstruction is at first of only slight degree, later becoming complete due to the development of edema. Bronchial closure is followed by absorption of air in the segment distal to the point of obstruction, causing it to become atelectatic and favoring, together with infection, the development of suppurative pneumonitis.[2] Associated thrombosis of the lobular blood supply contributes to the rapidity of tissue destruction.[11] As the pulmonary arteries are end-arteries, the peripheral areas, which have the poorest blood supply, are the first to undergo necrosis.[3] With the eventual involvement of a bronchial segment, air enters and a typical cavity forms. The degree of obstruction to free drainage will determine the extent of spread of the process and the development of chronic changes, consisting of loss of elastic tissue, fibrosis and eventual bronchiectasis in the surrounding lung tissue. With the complete occlusion of the communicating bronchus, rupture into the pleural cavity may result in the formation of a putrid empyema.[13] In some cases, small surrounding abscesses may coalesce to form an extensive multilocular cavity.[4]

TABLE I

Age	Incidence
0–9	1
10–19	1
20–29	7
30–39	10
40–49	10
50–59	13
60 plus	3
Total	45

Careful history-taking will usually elicit one or more etiologic factors, although it must be emphasized that these are often brought to light only by skillful direct questioning, as the patient is usually unaware of their significance. The following factors are of major importance:

(1) Any period of loss of consciousness profound enough to be associated with loss of protective pulmonary reflexes, leading to aspiration of secretions or foreign material.[9]

(2) Conditions leading to major impairment of normal pulmonary physiologic mechanisms. These may be primary, as in pneumonia or pulmonary infarction, or secondary, as in congestive heart failure.

(3) Acute or chronic infection in any portion of the upper respiratory tract.

(4) Miscellaneous situations in which the etiologic relationship is less obvious. Among these are included diabetes and alcoholism without definite history of an incident of coma; pulmonary venous stasis in mitral stenosis without systemic congestive heart failure or pulmonary infarction, and psychotic states.

TABLE II

Predisposing Factors

	No. Cases
1. Unconsciousness favoring aspiration	
a. Insulin shock therapy	1
b. Electric shock therapy	1
c. Hemorrhagic shock	1
d. General anesthesia	7
2. Local upper respiratory tract infections	
a. Oral sepsis and severe dental caries	16
b. Chronic tonsillitis	7
c. Acute or chronic sinusitis	7
d. Nonspecific upper respiratory infections	3
e. Dental extractions	2
3. Acute pulmonary pathology	
a. Bronchopneumonia	8
b. Lobar pneumonia	4
c. Pulmonary infection	1
d. Pulmonary edema (heart failure)	1
4. Miscellaneous	
a. Diabetes without history of coma	4
b. Alcoholism without history of coma	3
c. Mitral stenosis without congestive failure	1
d. Vomiting episode	4
e. Psychosis	1
f. Long occupational dust exposure	3
g. Chronic pulmonary fibrosis	1

The factors considered important in this series of cases are listed in table 2. A history of one or more was elicited in all but two cases. It should be pointed out that aspiration may occur in deep sleep, during which the gag and cough reflexes may be profoundly depressed.[5]

Presenting symptoms varied widely, according to the stage of development of the pulmonary lesion at the time of admission. The most common complaint was cough, which was usually productive and often blood-tinged. Two symptoms which have not received sufficient emphasis in the past are varying degrees of hemoptysis (a presenting complaint in half of this group),

TABLE III

Symptoms	No. of Cases
Cough	42
a. Productive	35
b. Dry	7
Localized chest pain	23
Hemoptysis	22
Fever	22
Weight loss	17
Night sweats	15
Malaise	7
Foul breath	6
Chills	5
Weakness	3
Dyspnea	2
Hoarseness	1
Hiccough	1
Cyanosis	1

and localized chest pain, which occurred with about the same frequency.[1] Chest pain is a manifestation of early pleural involvement. As fusion of the pleural surfaces later occurs, pain characteristically subsides, and its reappearance later on is frequently an indication of further pleural spread.[12] Table 3 lists the presenting symptoms of this group of patients in order of the frequency of their occurrence.

The duration of symptoms prior to admission varied from a few days to several months. This does not necessarily determine the age of the pulmonary abscess, but may mark instead the onset of a preceding upper

TABLE IV

Duration of Symptoms	No. of Cases
Less than 1 week	9
1–2 weeks	4
2–3 weeks	2
3–4 weeks	13
1–2 months	9
2–3 months	3
3–4 months	3
4–5 months	2

respiratory infection. The fact that 17 patients had gradually increasing difficulty for more than a month prior to admission indicates that in this group of patients the signs of progressing pulmonary infection were regarded too lightly. Smouldering bronchial infection following acute infections of the upper respiratory tract must be eradicated by continuing aggressive specific therapy and the careful marshalling of all available supportive measures. Table 4 groups the patients in this series with respect to duration of symptoms prior to hospitalization.

The importance of the individual's state of nutrition in determining his resistance to abscess formation is implied in table 5. This factor has received adequate emphasis elsewhere.

TABLE V

State of Nutrition	No. of Cases
Malnourished	23
Normal	15
Obese	7

Physical signs, particularly during the early phase of pulmonary involvement, are nonspecific and hence less helpful than other findings in making a diagnosis. The early signs are those of pneumonitis, atelectasis or infarction, depending on whether pulmonary infection, bronchial obstruction or vascular occlusion initiated the train of events.[5] As pointed out above, the pulmonary involvement commonly occurs next to a pleural surface in close contact with either the chest wall, interlobar fissure, diaphragm or mediastinum. The result is that signs of pleural irritation are frequently an early manifestation.[10] It is of interest to note that, while chest pain was

a prominent subjective complaint (in 23 cases), a friction rub was heard at the time of admission in only two cases. With the development of a complicating empyema there may be cyanosis, increasing dyspnea, spiking fever and more labored respiration, together with displacement of tracheal and mediastinal structures to the opposite side.[13] Chronic abscess formation, accompanied by pulmonary fibrosis, frequently leads to retraction of the chest wall on the involved side, with an increased contralateral expansion, and occasionally clubbing of the fingers and toes.[11] Physical findings at the time of hospital admission are recorded in table 6.

TABLE VI

Physical Findings	No. of Cases
Impairment to percussion	33
Moist râles	24
Impaired breath sounds	15
Splinting of the chest	11
Bronchial breathing	8
Local tenderness to percussion	3
Clubbing of the fingers	3
Friction rub	2
Essentially negative physical examination	4

Routine laboratory studies showed marked variability. Reports in the literature have described a consistent early elevation of the white blood cell count, although in fully half of our cases the initial counts were within normal limits (table 7).[9] About one-third of the patients had hemoglobin values below 11 gm., but in no case was it below 8 gm.

The character and amount of pulmonary secretions depend upon many factors, the most important being the size and location of the abscess, the degree of freedom of its drainage and the identity of its invading organisms. Foulness of secretions is due to the growth of anaerobic bacteria, which in

TABLE VII

Initial White Blood Count	No. of Cases
11,000 and below	23
11,000 to 16,000	10
16,000 to 20,000	6
20,000 and above	6

turn reflects the degree of obstruction to free drainage. On the basis of foul sputum or foul odor to the breath, we have divided the patients into "putrid" and "nonputrid" groups. This differentiation has probably been overemphasized in the literature, since it is dependent more upon the mechanics of drainage than on any basic etiologic difference. Adequate cultures were made in all but eight cases, and revealed a wide variety of organisms throughout both groups of patients. In every case, adequate examinations were made to rule out the presence of the tubercle bacillus. Spirochetes were found in only 12 cases, six times in association with fusiform bacilli, which were present in a total of nine cases. Samples examined

included both sputum and secretions aspirated at bronchoscopy. Thirty-three cases were classified as putrid and 12 as nonputrid. The organisms noted on smears and cultures are reported in table 8.

Routine chest stereograms have proved to be the most valuable single diagnostic tool in determining the presence and location of abscess cavities. Early findings may indicate only an undifferentiated pneumonitis, in which areas of increased radiolucence may later make their appearance. It is in this so-called "preabscess" stage that antibiotic therapy has its most effective use. Paradoxically, the efficiency of adequate therapy at this stage may make the detection of actual tissue necrosis impossible from a radiologic standpoint.

Only those cases in which cavitation was actually demonstrated are included in this report, and from the standpoint of prophylactic therapy they all must be regarded as clinical failures.

TABLE VIII

Organism	Total No. of Cases	"Putrid"	"Non-Putrid"
Spirochetes	12	10	2
Fusiform bacilli	9	8	1
Spirochetes and fus. bac.	6	5	1
M. catarrhalis	10	9	1
Non-hemolytic strep.	24	19	5
Staphylococci	8	5	3
Nonspec. gram-neg. bac.	8	6	2
B. pyocyaneus	5	4	1
Anaerobic streptococci	1	1	
Diphtheroids	3	3	
H. influenzae	1	1	
Pneumococci	4	3	1
No organism cultured	8	6	2
Total	45	33	12

Once cavitation is discernible, the differential diagnosis involves consideration of tuberculosis, malignancy with tissue necrosis, bullous emphysema, infected pulmonic cysts, diaphragmatic hernia, and abscess formation of specific etiology, as occurs in Friedländer or amebic infections. An encapsulated empyema occasionally confuses the picture.[6] Laminagrams are of value, particularly when the cavities are filled with sequestrum or are obscured by a dense surrounding pneumonitis.[14] Sectional films are sometimes necessary, and when lung detail is obscured by surrounding empyema, films done by the so-called "dense technic" may make the diagnosis when ordinary exposures are of little value.[11]

In the chronic stage cavities are characteristically thick-walled, and frequently circular areas of rarefaction appear within areas of diffuse fibrosis. This usually suggests the presence of a complicating bronchiectasis. In some cases thickening of the pleura is a common finding, with or without encysted empyema or pyopneumothorax.

Cavitation was demonstrated radiologically in 45 patients and proved at autopsy in the remaining one. This was accompanied by parenchymatous infiltration in 37 instances, lobar consolidation in eight and pleural effusion in five. Pneumothorax was noted once. The anatomic distribution of cavities is shown in table 9. In agreement with others, we found more

TABLE IX

Anatomic Location of Abscesses

Location	No. of Cases
Right upper lobe	16
Right middle lobe	2
Right lower lobe	11
Right lung—total	29
Left upper lobe	14
Left lower lobe	2
Left lung—total	16

abscesses located in the right lung.[4] Our series differed from most, however, in that the upper lobe abscess outnumbered those found in the lower lobes.[7]

Bronchoscopy was performed on 19 patients, the majority of these being done during the past four years. Multiple bronchoscopies were done in

TABLE X

Case No.	Bronchoscopic Finding	Location	Abscess Location by X-Ray
5	Pus and inflammation	Trachea, lt. main, lt. upper	Left upper
37	Pus and inflammation	Right main	Right middle
7	Pus and inflammation	Left main, lt. upper	Left upper
31	Pus and inflammation	Left main	Left lower
34	Pus and inflammation	Left main	Left lower
40	Pus and inflammation	Right upper	Right upper
13	Pus and inflammation	Right upper	Right upper
14	Pus and inflammation	Right upper	Right upper
29	Pus and inflammation	Right upper	Right upper
16	Pus and inflammation	Right upper	Right upper
3	Pus and inflammation	Right middle and lower	Right lower
44	Pus and inflammation	Right middle and lower	Right lower
23	Pus and inflammation	Right middle and lower	Right lower
15	Inflammation alone	Left main, lower, upper	Left upper
10	Inflammation alone	Left main, lower, upper	Left upper
45	Inflammation alone	Right middle and upper	Right upper
11	Inflammation alone	Right middle	Right lower
30	Inflammation alone	Right lower	Right middle
26	Inflammation alone	Left lower	Left lower

three instances. Table 10 lists the bronchoscopic findings, together with the ultimate localization of the lesion as determined by roentgen-ray or postmortem examination. It is thus evident that bronchoscopy is an important aid for determining the presence and location of bronchial obstruction and for obtaining uncontaminated secretions for laboratory examination.

TABLE XI

Conservative Arsenic Sulfa	Surgery	Deaths	% Mortality	Average Morbidity in Months
26	9	4	15.5	6.18
Penicillin 11	4	1	9.1	5.2
Primary Surgery 8	8	0	0	16.25
45	21	5		Average for series 7.3 mos.

The results of various therapeutic approaches to individual cases are shown graphically in table 11. A changing medical and surgical armamentarium and the extreme variability in pathology encountered explain its lack of uniformity. As a result, in none of the therapeutic groups are there sufficient patients to permit statistical evaluation of any single measure.

Table 11 compares the results of the group treated by conservative methods alone, by arsenic and by sulfonamides with those obtained by penicillin therapy and primary surgical approach. Nine of the 26 cases treated medically in the era before penicillin eventually came to surgery, with four deaths resulting. There was only one death in the penicillin group of 11 cases, four of which were eventually operated upon. In the group of eight cases treated with surgery alone there were no deaths, but a high incidence of complications occurred, with a resulting average morbidity of 16.25 months in the six in which the length of postoperative follow-up was adequate. This was approximately three times the average morbidity found in the other groups.

Acute and chronic abscesses are not separately classified, though it will be noted from table 4 that seven patients had symptoms for periods longer than two months prior to hospitalization.

Five patients died under observation (11.1 per cent). In five more the period of follow-up study was insufficient to determine the final outcome, although in one of these cavitation was still present 16 months after its discovery. The remaining 35 patients recovered, with periods of disability ranging from 15 days to 45 months.

Table 12 compares the mortality from lung abscess in this institution over the past 35 years. The figures for the first two periods are taken from

TABLE XII

Deaths from Lung Abscess

Period	Cases	Mortality
* Before 1931	50	42%
* 1931 to 1936	50	26%
1936 to 1942	23	17.7%
1942 to present	22	4.5%

* Allen and Blackman.[1]

TABLE XIII

Type of Therapy

Case	S*	Arsenic	Sulfa**	Antibiotic***	Surgery	Morbidity	Result	Complications
1	X					2 mos.	Dead	Massive hemorrhage.
2	X					7 days	Dead	
3	X					16 mos. U.F.	Alive	Abscess still present.
4	X					15 days	Well	
5	X					3 mos.	Well	
6		1.8 gm. 7 da.				2 mos.	Well	
7		4.0 gm. 14 da.				4½ mos.	Well	
8		1.8 gm. 9 da.				1 mo.	Well	
9		10.5 gm. 60 da.				3 mos.	Well	
10			32 gm. 8 da.			5 mos.	Well	
11			14 gm. 2 da.			4 mos.	Well	
12			86 gm. 19 da.			5 mos.	Well	
13				1.6 aerosol 16 da. 34.4 IM 114 da.		5 mos.	Well	Uncontrolled diabetes.
14				2.4 IM 15 da. 0.9 aerosol 18 da.		6 mos.	Well	
15				10.75 IM 19 da. 6.0 IM 15 da. 0.8 aerosol 8 da.		8 mos.	Well	
16						4½ mos.	Well	
17					One stage drainage (2nd stage unsuccessful).	2 mos. U.F.	Alive	Chest wall abscess.
18					One stage drainage.	5 mos. U.F.	Alive	Bronchopleural fistula, empyema.
19					Six attempts at drainage.	46 mos.	Well	Bronchopleural fistula.
20					Subphrenic exploration.	7 mos.	Well	P. o. empyema.
21					Two stage drainage, repair of fistula.	9½ mos.	Well	Pleural fistula.
22					Two stage drainage.	7 mos.	Well	
23					Two stage drainage, phrenic crush insert, intercostal tube.	12 mos.	Well	Bronchopleural fistula, empyema.
24					Two stage drainage, plastic repair of fistula.	16 mos.	Well	Bronchopleural fistula.
25		3.0 gm. in 5 da.	27 gm. in 3 da.			2 mos.	Well	
26		4.6 gm. in 8 da.	33 gm. in 5 da.			3 mos.	Well	

S* Supportive only. Sulfa** Doses refer to diazine and thiazole except as noted. U.F. Unsatisfactory follow-up.
Antibiotic*** Doses in million units of penicillin except as noted. I.M. Intramuscular.

TABLE XIII—*Continued*

Antibiotic*** Doses in million units of penicillin except as noted. I.M. Intramuscular.

TABLE XIII—*Continued*

Case	S*	Arsenic	Sulfa**	Antibiotic	Surgery	Morbidity	Result	Complications
27		Meph. 0.2 gm. —5 da.	36 gm. in 8 da.			2½ mos.	Well	
28			4 gm.	3.3 aerosol 31 da. 4.46 IM 33 da.		2 mos.	Well	
29		0.9 gm. in 3 da.	26 gm. in 6 da.	3.36 IM 7 mos.		7 mos.	Well	
			288 gm. Merazine in 72 da.					
30		Meph. 0.12 gm. in 2 da.	48 gm. in 8 da.	3.3 IM 33 da. 1.65 aerosol 33 da.		4½ mos.	Well	
31		3.6 gm. in 9 da.			Two stage drainage.	7 mos.	Well	
32		0.6 gm. in 1 da.			Phrenic crush.	10 mos.	Well	
33		0.6 gm. in 1 da.			Two stage drainage.	3 mos.	Dead	
34		2.4 gm. in 7 da.			Two stage drainage.	U.F.	Alive	
35			Pyridine 36 gm. in 6 da.		One stage drainage. Excision of broncho-pleural fistula.	24 mos.	Well	Bronchopleural fistula, empyema, bronchiectasis.
36			45 gm. in 7 da.		One stage drainage.	5½ mos.	Well	Bronchopleural fistula.
37			30 gm. in 5 da.		Thoracotomy.	3 mos.	Dead	
38				2.4 IM in 8 da.	RU lobectomy.	5 mos.	Well	
39				0.16 IM in 2 da.	Thoracotomy.	2 mos.	Dead	Brain abscess.
40		5.4 gm. in 6 da.	30 gm. in 5 da.		One stage drainage of chest wall abscess 2 X.	10 mos.	Well	Chest wall abscess.
41		2.4 gm. in 3 da.	Diazine 27 gm. in 6 da.		Drainage of empyema.	8 mos.	Well	Bronchopleural fistula.
			Pyridine 9 gm. in 3 da.					
42		2.4 gm. in 4 da.	54 gm. in 6 da.		Unsuccessful one stage drainage.	5 mos.	Well	
43		0.6 gm. in 3 da.	Neoprontosil in 8 da.		One stage drainage; 4 unsuccessful attempts at 2nd stage.	14 plus mos. U.F.	Alive	
44			18 gm. in 3 da.	Penicillin 12.5 IM 32 da.	Two stage drainage.	3 mos.	Well	
				Streptomycin 44.0 gm. 11 da.				
45		3.6 gm. in 4 da.	36 gm. in 6 da.	1.0 IM 10 da.	One stage drainage.	7 mos.	Well	

Allen and Blackman.[1] Credit for the progressive decrease in mortality is due not only to chemotherapy and the antibiotics but also to improvement in surgical technics.

Table 13 summarizes treatment and results in each case of the present series.

The commonest surgical complications were fistulae, empyema and abscess of the chest wall. All of these were handled satisfactorily by further surgical procedures, but their occurrence contributed substantially to prolongation of morbidity. Bronchiectasis was demonstrated in only two cases, though its presence was suspected in several others. Brain abscess and massive hemorrhage each occurred once, and were the immediate cause of death in the respective cases.

Comment

As mentioned above, satisfactory management of lung abscess requires constant reëvaluation by a medical team consisting of internist, radiologist, bronchoscopist and thoracic surgeon. Dependence upon the duration of the disease process alone as the criterion for surgical intervention will result in many failures.

When sufficient data have been accumulated to permit adequate statistical evaluation, it will doubtless be found that both sulfonamides and the antibiotics have been effective in increasing the incidence of so-called "medical cures." This should not, however, cause one to lose sight of the fact that the cardinal principle in treatment of lung abscess is the achievement of adequate drainage, once actual parenchymal lysis is evident. If adequate drainage does not occur spontaneously, or cannot be assured by postural means or by bronchoscopy, medical measures alone will not suffice. If one then persists in their use beyond the optimal time for surgical intervention, great harm may be done.

While antibiotics are of value in combating the element of infection in the fully developed case, it must be emphasized that their greatest potential in this disease rests in their routine prophylactic employment in those situations where pulmonary atelectasis or infarction has occurred or is likely to occur. This applies particularly to those situations over which the physician normally exercises close control. All hospitalized patients who have undergone general anesthesia, convulsive states or coma should be given bacteriostatic doses of penicillin for a minimum of 48 hours, or until they have been afebrile for 24 hours.

In recent years the usefulness of bronchoscopy in the treatment of lung abscess has become generally accepted, but the prophylactic value of this procedure should receive greater emphasis. Bronchoscopy will often serve to prevent abscess formation in the presence of atelectasis or of so-called "unresolved pneumonia." Occasionally unsuspected foreign bodies will be encountered and removed, and those cases secondary to malignancy will

meet with earlier recognition through the examination of biopsy specimens and secretions by the Papanicolaou technic. In the fully developed case the bronchoscopist may establish and maintain drainage by aspiration of debris and by the mechanical removal of granulation tissue.[15] Repeated bronchoscopies are indicated if they seem to aid drainage materially in the individual case, and if this opinion is supported by satisfactory roentgen-ray evidence.

Once the diagnosis is established, frequent progress roentgenograms are required to evaluate the changing state of the lesion as reflected in reduction of cavity size and decrease of its surrounding area of pneumonitis. This is to be emphasized in view of the fact that, with the use of large doses of penicillin, the clinical course of the patient and the character of the

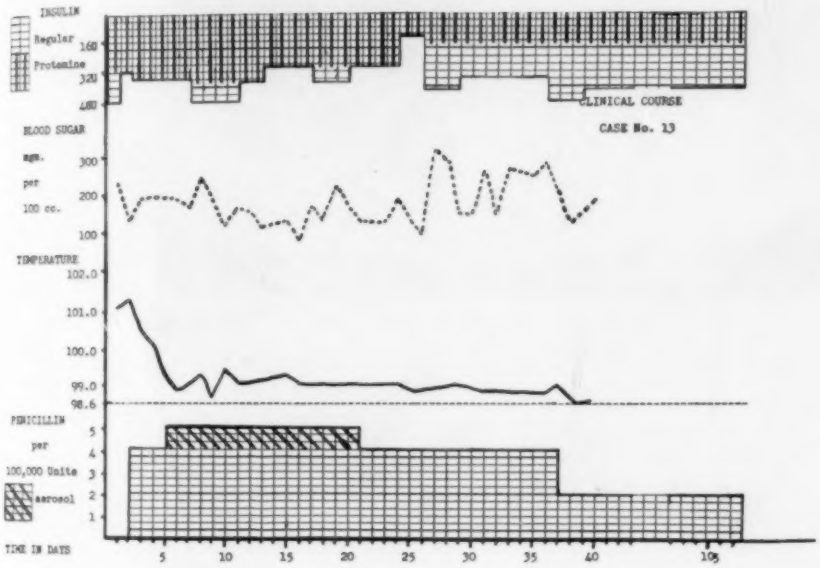


FIG. 1.

sputum may be deceptive. Surgery is safely and advisably delayed if the disease process shows steady and continuous improvement under medical management. Figure 1 represents the progress of case 13. His roentgenograms, shown in figures 2 through 10, show satisfactory resolution of an abscess treated medically. Many early cases can be handled in this manner, though it must be reëmphasized that medical treatment with antibiotics will meet with success only when adequate drainage is present.

The intramuscular injection of 100,000 or more units of crystalline penicillin in aqueous solution every three hours has been the preferred method of administration in early cases. Penicillin aerosol has been utilized in addition to parenteral dosage in more advanced cases, where infected tissue has been more completely deprived of its blood supply. Intratracheal

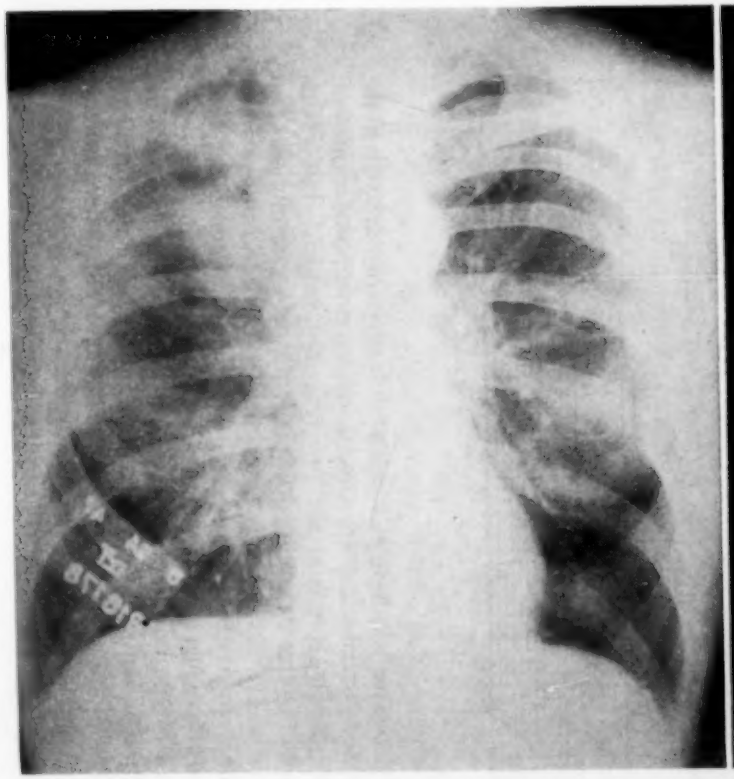


FIG. 2.

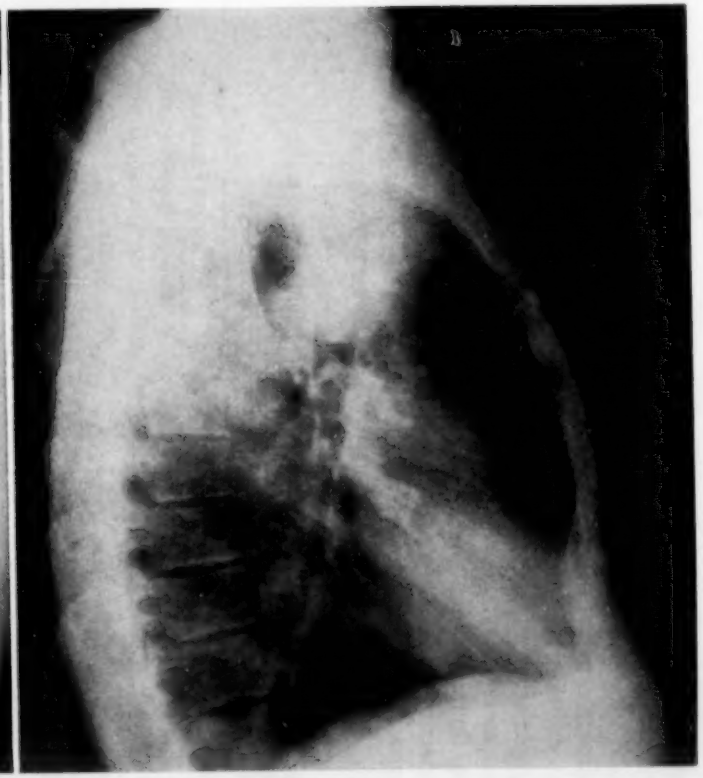


FIG. 3.

FIG. 2. Admission film—area of increased density in the right upper with central excavation. *Case 13.* White male, age 39, known diabetic, taking 32 units of protamine zinc insulin daily. Patient treated for acute coronary occlusion five years prior to the present illness.

C.C. Attack of "flu" two months previously, followed by right-sided chest pain aggravated by respiration. Cough with production of up to one-half pint of "phlegm" daily. Increasing anorexia with vomiting for three days prior to admission. No hemoptysis.

PX. Chronic sinusitis. Few moist râles at right apex and in right infraclavicular area. Otherwise negative.

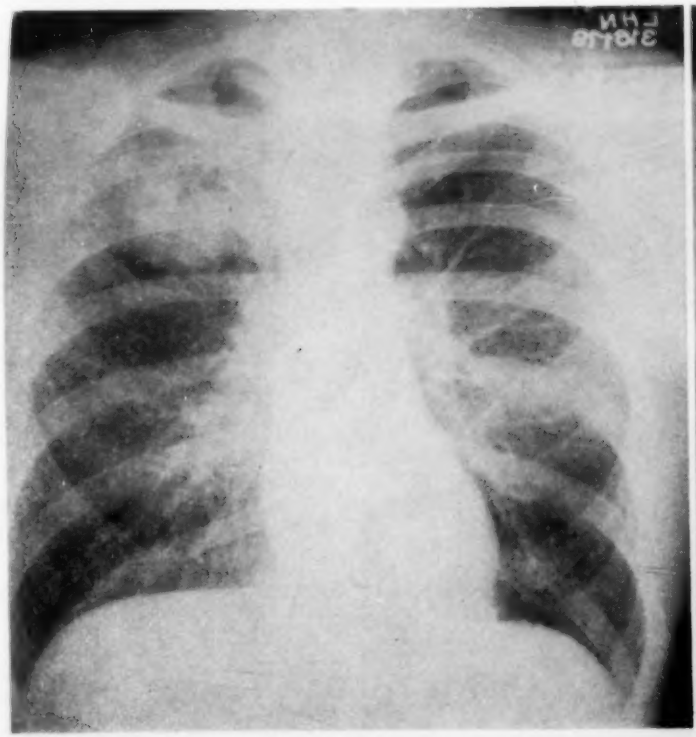
FIG. 3. Right lateral, two days after admission, showing area of increased density near the apex with central radiolucency. It lies midway between the sternum and the spine.

Lab.: Tbc. skin test negative. Urine: sugar and acetone present. W.B.C., 11,800. Sed. rate, *27* mm. in one hour. Sputum, no acid fast. *Staph. aureus, M. catarrhalis,* Monilia.

Roentgenogram: Massive consolidation of right upper lobe, apical area with cavitation in the same area.

way between the sternum and the spine.

Lab.: Tbc. skin test negative. Urine: sugar and acetone present. W.B.C., 11,800. Sed. rate, 27 mm. in one hour. Sputum, no acid fast. *Staph. aureus, M. catarrhalis,* Monilia.



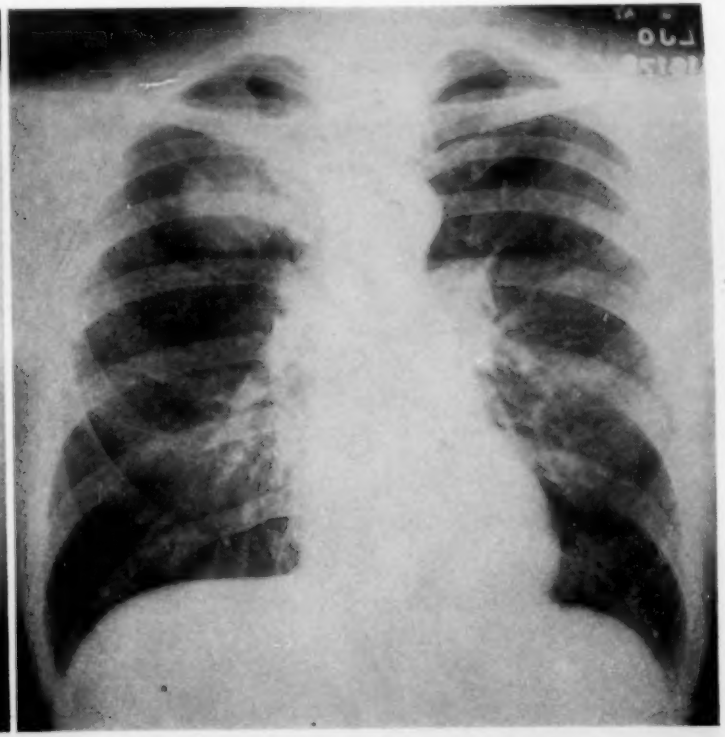


FIG. 4.

FIG. 5.

FIG. 4. Ninth day. Slight increase in size of the area of increased density in the right upper lobe (this in spite of definite clinical improvement). There is evidence of a definite fixed division in the center.

FIG. 5. Seventeenth day. Definite decrease in the size of the lesion in the right upper chest. There is no evidence of excavation at this time.

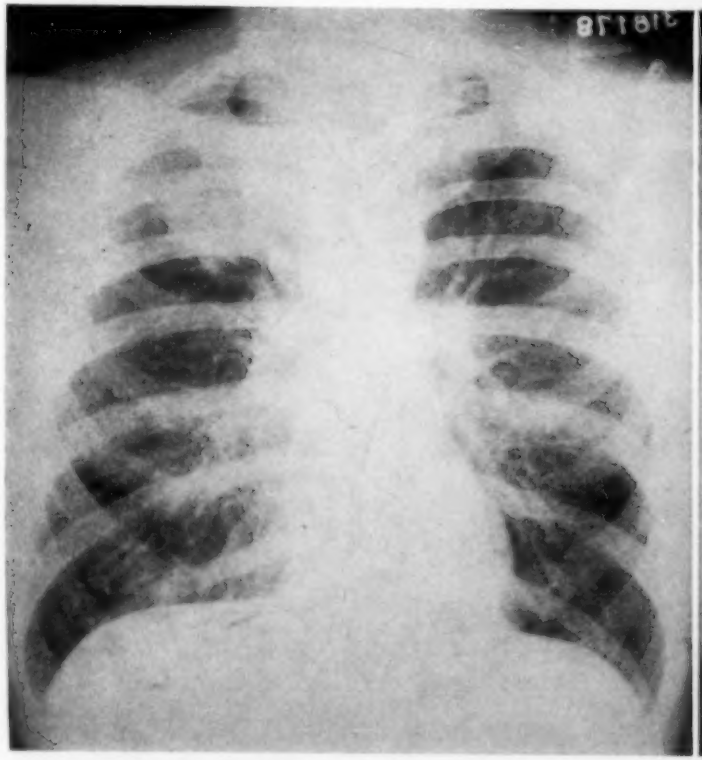


FIG. 6.

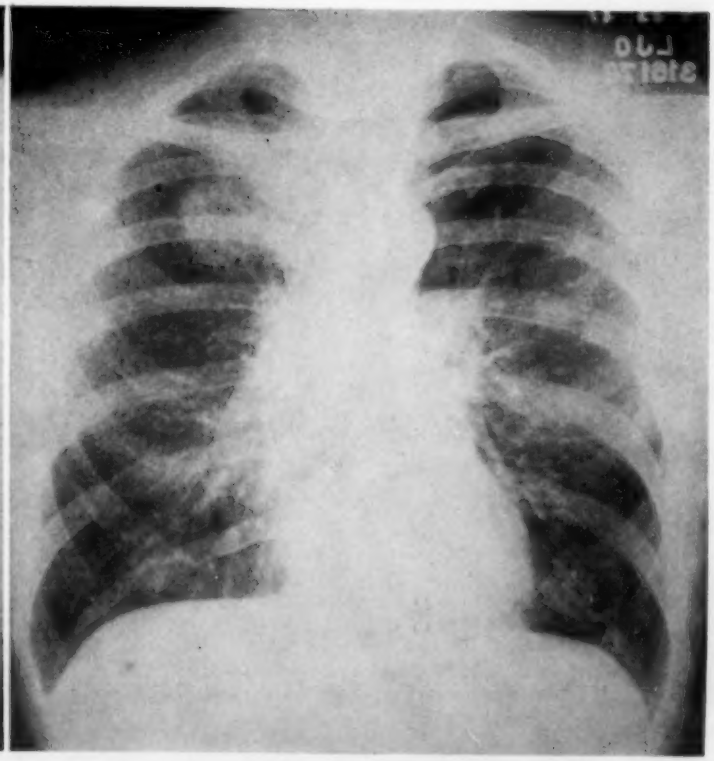


FIG. 7.

FIG. 6. Twenty-third day. The area of increased density in the right upper is somewhat smaller but the change is not marked. There is slight hazing lateral to the lesion which may be due to some pleural involvement or to atelectasis in the peripheral zone of the lung. There is no definite evidence of excavation within the circumscribed lesion.

FIG. 7. Thirtieth day. The area in the right upper is showing continuing resolution. It is considerably smaller than at the time of the previous examination.

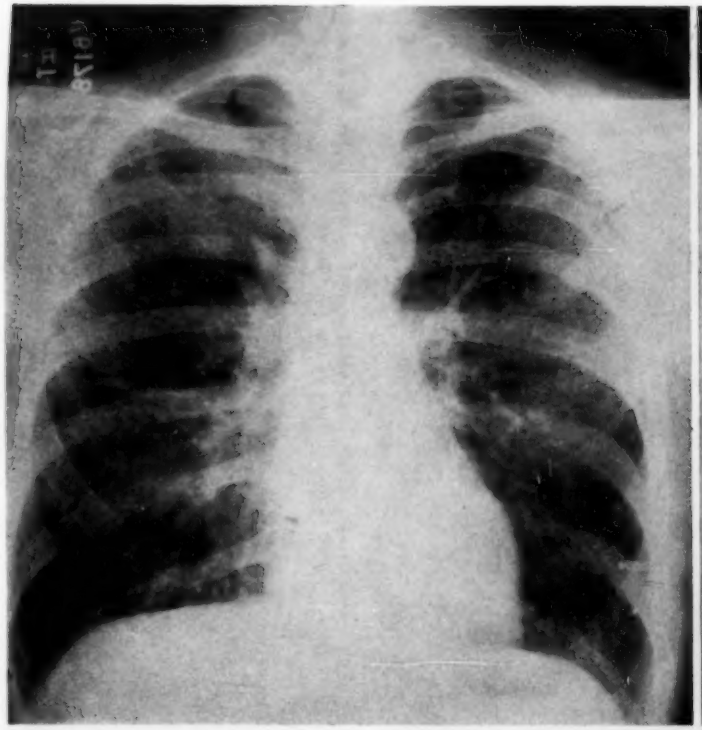


FIG. 8.

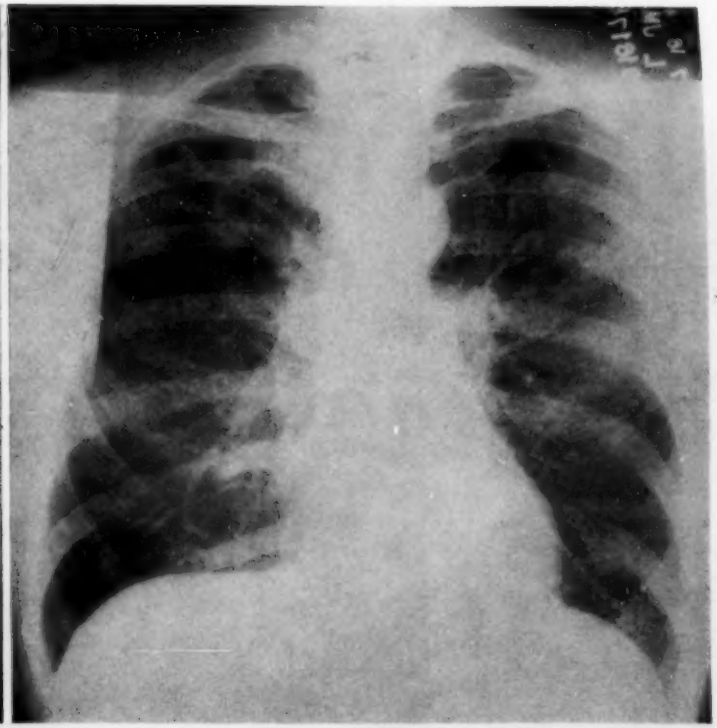


FIG. 9.

FIG. 8. Thirty-seventh day. Continuing decrease in size of the lesion in the right upper. The entire area shows a decrease in density.
FIG. 9. Fifty-third day. Small area of infiltration in the right upper remains. There may be a small area of decreased density in the center of this region, probably representing the remains of a cavity.

instillations of solutions of penicillin advocated by Metras and his co-workers have not been employed, since they tend to interfere with drainage.[9] Sulfonamides or other antibiotics should be used to supplement or replace penicillin in those cases where in vitro sensitivity studies demonstrate the presence of penicillin resistant organisms. Arsenotherapy has been displaced by the use of penicillin, since the latter is effectively spirochetocidal in addition to its bacteriostatic activity against the more commonly encountered pyogens.

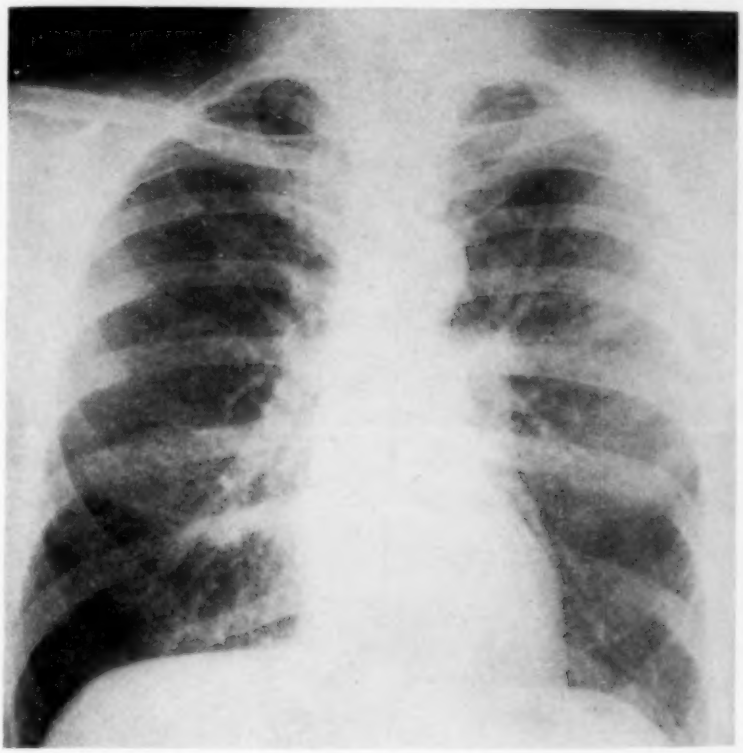


FIG. 10. One hundred second day. There is a very minimal increase in the markings in the right upper lung field. There is no evidence of the abscess cavity previously reported.

If progress roentgenograms fail to show continued regression, surgical intervention is indicated.[12] Even if the advance of the lesion has been apparently stopped, it must be remembered that after about six weeks the effects of the disease process will leave their permanent mark on the involved lobe in the form of scarring, fibrous retraction and bronchiectasis, with consequent serious reduction in the functional efficiency of the involved segment.[10] In such situations, more harm is done by delaying operation than by premature interference. It is not within the scope of this com-

munication to discuss the surgical approach to treatment, though our present appreciation of the amount of lung damage existing in longer standing lesions makes it appear that lobectomy will enjoy increasing popularity.

Summary and Conclusions

Forty-five proved cases of lung abscess observed as in-patients during the past 10 years are analyzed and the results of therapy presented.

Three conditions considered necessary for the formation of a lung abscess are infection, bronchial obstruction with resulting atelectasis, and impairment of the arterial circulation to the segment involved.

Predisposing clinical states may be divided into four groups: those conditions resulting in loss of protective pulmonary reflexes and thus favoring aspiration; local situations in the mouth or upper respiratory tract favoring infections; acute pulmonary pathology, and certain miscellaneous conditions including diabetes, alcoholism and some forms of heart disease.

Two presenting complaints which have heretofore received insufficient emphasis, namely, hemoptysis and localized chest pain, are emphasized and the variability of the physical signs is cited, while the place of roentgen-ray and the bronchoscope as diagnostic tools is discussed.

It is believed that the importance of dividing cases into a putrid and a nonputrid group, according to the organisms isolated and the clinical character of the sputum, has been overemphasized, since the quality of the sputum is merely a reflection of the degree of obstruction to drainage existing at the moment. It is important to rule out the presence of tubercle bacilli, especially in upper lobe cavities, which formed 65 per cent of our group.

The cardinal principle in therapy should be establishment of drainage, and where this is not accomplished all other therapeutic efforts will be doomed to failure. Penicillin in large doses should be employed in all cases, but the chief usefulness of this antibiotic will be aborting cavity formation during the "pre-abscess" stage. For this very reason, the true value of penicillin may be difficult to prove statistically but may rather be shown by the decreasing incidence of lung abscess as a complication in respiratory disease treated with antibiotics. Surgery should not be withheld if frequent progress films fail to reveal consistent diminution of cavity size in addition to clinical improvement. After six weeks, complications including fibrosis and bronchiectasis will make serious inroads on the functional efficiency of the involved lung segment, and it seems logical to assume that lobectomy will enjoy increasing popularity. In those cases in which surgery is delayed, the increase in mortality and morbidity will be significant.

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A STUDY OF THE USE OF RADIOACTIVE GALLIUM IN MEDICINE*

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I. INTRODUCTION

THIS study was initiated to determine whether or not radioactive gallium would prove to be of value as a method for radio-isotope tracer studies and/or as a therapeutic measure in the management of patients who have primary or metastatic malignancy of the bone. It was conducted conjointly in the U. S. Naval Medical Research Institute and in the Laboratory of the Radioactive Isotope Board, U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland. Both of these activities are integral parts of the National Naval Medical Center, Bethesda, Maryland.

The preliminary work on the metabolism and toxicity of gallium was done by Commander H. C. Dudley (MSC), U. S. Navy, and his co-workers in the laboratories of the U. S. Naval Medical Research Institute. The work on the use of radioactive gallium in human pathologic conditions was performed in the Radioactive Isotope Laboratory of the U. S. Naval Hospital, Bethesda, Maryland. This activity functions under the supervision of the "Committee for Human Application of Radio-isotopes," of which the author is senior member.

This study on the human use of radioactive gallium was decided upon when the work of Dudley et al. on laboratory animals, using nonradioactive gallium, revealed the following interesting features concerning the nonradioactive form of this element: (1) In the form of its lactate salt it is very quickly absorbed following intramuscular injection. (2) It is rapidly transported to and deposited in the bony structures of the body. (3) It is excreted extremely slowly. (4) While retained in the animal body for a long period of time, it is relatively inert and nontoxic, at the dosage levels required for radio-isotope tracer studies and also at that dosage estimated to provide sufficient radioactivity for attempting eradication or control of bone malignancies. (5) It produced no demonstrable pathologic effects on brain, liver, kidneys or, in fact, any other organ or system of the bodies of laboratory animals. Hence it appeared that here was a likely possibility of adding a new radio-isotope to the list of those already in use in medicine.

A review of the literature disclosed very little concerning gallium since

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The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

its discovery. It has always been considered a rare metal. However, in recent years, new methods have reduced considerably its cost of production. Gallium has an atomic number of 31, an atomic weight of 70.1, and its symbol is Ga. It was discovered in 1875 by Lecoq de Boisbandrau by means of spectrum analysis. He found the element in zinc blends from the Pyrenees. It is widely distributed in nature, although present only in minute quantities. It is found frequently in iron ores and in bauxite. It is a hard brittle metal of bluish-white color which melts at 29.75° C.

Sollman [1] reports but two references to gallium listing its activity under that of the rare earth metals. He compares it to aluminum in its toxicity, and states it resembles that element in its pharmacologic properties.

II. Studies on the Metabolism of Gallium

Dudley developed a reliable and acceptable analytic method for the determination of gallium in tissues and excreta. This is given in detail in reference 2, and was used to study the gallium content of the tissues of rats and other animals following single sublethal injections of gallium lactate.[2] Two or more of the animals so injected were killed at stated intervals from four hours to 180 days following the subcutaneous injection of 100 mg. of gallium per kilogram of body weight. Duplicate determinations of gallium content (nonradioactive) were done on the liver, kidney and femurs of each animal. That study revealed that the gallium is quickly absorbed and rapidly deposited in the bones of the animals. It revealed that gallium is retained in the bones in appreciable amounts for more than 90 days. The liver and kidneys, on the other hand, while having moderate initial concentrations, rapidly lost most of the gallium, and there was very little remaining in those organs at the end of 30 days.

Work was done with other laboratory animals to determine if there was any species variation.[3] Rabbits were injected with gallium lactate in doses of 90 to 100 mg. of gallium per kilogram of body weight. The urine and feces of these animals were studied to determine the degree of excretion of gallium. It was learned that: (1) Gallium rapidly makes its appearance in the urine at a high level, but this drops rapidly and at the end of three days reaches a constant rate at a low level of less than 1 mg. of gallium per day. (2) Very little gallium was found in the feces, and it seems probable that this small amount was due to contamination of the feces by the urine. (3) It was learned that, as with the rats, the rabbits retained over 85 per cent of the gallium lactate injected subcutaneously after a single dose of 90 to 100 mg. per kilogram of body weight. At the end of 10 days most of this was found deposited in the bones. This confirmed the findings with rats and again indicated that practically all of the gallium was deposited in bones and is released very slowly.

Further study of gallium content of bone of rats and rabbits showed that both the soft marrow and periosteum contain approximately the same

gallium content as muscle (2 to 6 parts per million), whereas the cortex of bone contained 50 to 150 parts per million. The trabecular bone is still richer, having been found to contain from 100 to 300 parts per million. Again the astounding discovery was made that this disposition of gallium occurs in large part within four hours of a single subcutaneous or intramuscular injection of gallium lactate, and is carried to completion within 24 hours of the injection.

Again using a series of laboratory animals, Dudley and his co-workers [3] studied the gallium content of both whole blood and plasma following single subcutaneous injections of gallium lactate. As was shown above, the blood gallium levels rose rapidly, reached a peak, and subsided to a very low level within four hours. At the end of four hours only 1 to 3 micrograms were found in the plasma. From 24 hours to 14 days following a single dose injection, the plasma levels dropped from 2 parts per million to 0.2 part per million.

Washed blood cells revealed that none of the gallium was present at any time during this study. Rabbits injected with near-lethal doses of gallium and also with lethal doses showed no permanently significant or marked changes in the formed elements of the blood. Occasionally there was seen a decrease in lymphocytes and an increase in segmented cells in 24 to 48 hours, but these changes rapidly returned to normal after 48 hours.[3]

Using radioactive gallium to study further the physiologic activity of this element, Dudley and Maddox [4] demonstrated by the use of radioautographs that it entered bone at a rapid rate, and became localized there in the areas of greatest osteogenic activity. Dudley et al. then combined chemical and radiologic studies on the distribution and excretion of gallium in experimental animals following the subcutaneous injection of radiogallium (Ga^{72}) as its citrate salt.

Determinations of Ga^{72} in samples of tissues and excreta were carried out by (*a*) gamma counting technics, using an end window Geiger-Müller tube, and (*b*) making radioautographs of sections of tissues.

By these methods, Dudley and his co-workers have determined with accuracy that the distributions of gallium in the various experimental animals used were very consistent as to location. In dogs, rats, rabbits and mice, the bones picked up by far the greatest amount. Next in order of magnitude came the kidneys. These contained less than 50 per cent of the gallium content of the bones. In descending order, using the bone content of gallium as 100 per cent, came liver (14 per cent of bone content); red marrow (6 per cent of bone content); spleen (4.4 per cent of bone content), and muscle (1.1 per cent of bone content).

The above concentrations indicate the possibility of damage to the kidneys in using inert gallium and radioactive gallium in dosages approaching the LD 50 level. Hence, further observation on this was made. With the use of gallium in near lethal dosages, some animals did develop albumin-

uria, casts and glycosuria. However, these findings developed only at very high and toxic dosage levels, which were far above the dosages which would be required for the use of radioactive gallium in human cases.[5]

The results of these studies on the metabolism and distribution of gallium following subcutaneous injections of the citrate show that, in the rat, rabbit and dog, only bone and kidneys receive significant amounts of the element. No appreciable persistent concentrations occurred in other soft tissues. Following subcutaneous injections of Ga^{72} as the citrate, the rabbit excretes 30 to 55 per cent of the total dose in the urine within 16 hours, while the osteoid tissues absorb an additional 30 to 48 per cent within the same period of time. The liver and kidneys fix small but appreciable quantities of gallium where it is retained in part for more than 30 days. However, on autopsy, no pathologic changes of these organs could be demonstrated. Gallium enters the bones rapidly in less than four hours and is retained in fairly large amounts for more than 90 days. Gallium is transported by the plasma, but largely disappears therefrom within 24 hours. The mode of injection influences markedly the initial plasma gallium levels. Intravenously, the plasma gallium is initially increased and drops rapidly during the first six hours, while subcutaneous injection produces only a moderate plasma concentration, which falls slowly to a constant figure at the end of 24 hours. No permanent significant changes were observed in the formed elements of the blood in laboratory animals following injection of fatal or near-fatal amounts of nonradioactive gallium lactate.

In summarizing the results of studies on the metabolism of gallium, it is evident that this element is an avid bone seeker [4] and exhibits promise of becoming a new tool in the study of bone metabolism and perhaps in the therapy of certain of the diseases of the bones.

III. Studies on the Toxic Action of Gallium

Rabuteau [6] reported that in the frog, injections of gallium chloride, or of the ammonium gallium complex ($NH_4Ga(SO_4)_2$), produced an increased excitability, followed by weakness, paralysis and death in a few days. Doubling this dosage produced these effects in a few hours.

Schwarz and Sicke [7] demonstrated that in mice a single subcutaneous injection of 10 mg. per kg. of ammonium gallium sulfate were sufficient to cause death. In rats, using the same salt, 20 mg. per kg. were necessary to produce 100 per cent fatality, while in rabbits, 100 mg. were necessary to be 100 per cent lethal. Levaditi and co-workers [8] reported that in rabbits, when using dosages of 30 to 45 mg. of gallium tartrate per kilogram of body weight given intramuscularly, death occurred within four hours. In the light of subsequent studies it seems likely that the toxic manifestations were in some degree the result of the tartrate ion.

Meek, Harrold and McCord [9] have made the most comprehensive study of gallium toxicity up to the recent studies of Dudley and his co-workers.

The former group used the nitrate salt as test material. They found that in both man and animals, skin patches containing this salt produced no reactions. In animals, the intravenous injection of 16 mg. per kilogram of body weight produced no gross evidence of damage. These workers found that in rats, 6 mg. of gallium per kilogram of body weight likewise caused no effects, while one intravenous injection of 72 mg. of gallium per kilogram of body weight caused delayed effects and death in seven to 14 days with acute nephritis.

Dudley et al.[10] showed that the tartrate, chloride and ammonium complex ($NH_4Ga(SO_4)_2$) salts of gallium in vitro were very efficient protein precipitants, and that the chloride and nitrate salts of gallium were almost completely and rapidly precipitated as the gelatinous hydroxide at pH 7.4. Obviously these salts were unsatisfactory for injection. Since lactic acid is nontoxic, they decided to further the studies, using the lactate salt of gallium for injection purposes.

These same workers [10] reported on studies of the toxicity of gallium in laboratory animals by inhalation (aerosol), diet and injection methods. Exposure of rats to gallium chloride aerosol in concentrations of from 18.4 to 94.4 mg. of gallium per milliliter of air for periods varying from 30 to 240 minutes failed to cause death. However, on autopsy, each animal showed some degree of lung consolidation. Also, it was discovered that no gallium passed the alveolar membranes of the lungs.

In an effort to study the toxicity of gallium when introduced through the gastrointestinal tract, four series of young rats (initial weights, 105 to 140 gm.) were fed for 13 weeks on diets containing gallium chloride in concentrations of 10, 100, 500 and 1,000 parts of gallium per million of feed. There was no evidence that the presence of gallium in the food produced any effect whatsoever. The animals' conditions were excellent and their weight curves paralleled those of the normal controls. There were no deaths among the 40 rats in this study or among the 20 controls.

Chemical examinations of the tissues of these animals revealed no detectable amounts of gallium in the livers, spleens or kidneys after the completion of 13 weeks of such feedings. The bones were found to contain tracer amounts. These studies indicate that in rats there is little or no absorption of gallium from the intestinal tract, although the average daily intake was as high as 20 mg. of gallium per kg. per animal.[11] Apparently the alkalinity of the intestinal tract is sufficient to convert the soluble chloride into the insoluble hydroxide or into some other insoluble compound.

In order to provide a stable salt at the pH of the intestinal tract, gallium lactate was then studied in the diet of rats.[10] This salt is stable at the pH range of 7.0 to 7.6. Two series of young rats (initial weights, 88 to 112 gm. were fed for 26 weeks on diets containing gallium lactate in concentrations of 500 to 1,000 parts per million of feed. Each series consisted of 20 rats (10 males and 10 females), with an equal number of pair fed controls.

These groups were fed on sufficient commercially prepared diet to yield normal growth curves.

The 20 rats receiving the 0.5 gm. of gallium per kilogram of food (500 parts per million) gained 177 per cent in weight during the 26 weeks of feeding. The controls showed 192 per cent gain in weight during the same period. Aside from these slight differences in average weight curves, no other effects were noted in these animals. Chemical examination of the tissues of the animals fed gallium lactate at a level of 15 to 20 mg. per kg. of gallium per day (1,000 parts per million of food) showed that there were traces of gallium in the liver, spleen and kidneys, while the bone contained amounts from 1 to 3 micrograms per gram of tissue (1 to 3 parts per million). These studies revealed, therefore, that gallium in a form soluble at pH 7.6 is not readily absorbed from the intestinal tract. Therefore, it can be concluded that, in general, gallium compounds offer little hazard from the standpoint of an ingested poison.[10]

Dudley and his colleagues, working with rabbits, reported [10] that intravenous dosages of gallium lactate in excess of 43 mg. per kilogram of body weight were necessary to kill the animals, whereas doses of 92 mg. per kilogram of body weight (or higher) of the lactate were required to produce death of the animal when given subcutaneously. Such deaths, seemingly from respiratory failure, were preceded by a flaccid paralysis, especially of the lower extremities. No other particular neurologic symptoms or findings were observed. Gross autopsy findings were essentially negative, except for the lungs, which were often found to be edematous and hemorrhagic.

In work with rabbits, it was learned that the initial concentration in the kidneys was not so great as in the rats. The most striking finding in studying the effects of gallium in these animals is the shift in the higher gallium content from the kidney to the spleen and liver in the rabbits killed 60 days after injection.[10] This shift seems to be due to clearance by the kidney into the urine, since all of the studies with every type of laboratory animal indicated that the urine is the main vehicle of excretion.

The blood urea nitrogen of another series of 25 rats was studied following injection of gallium lactate both intravenously and subcutaneously. In those rats which died within 24 hours following injections of gallium lactate, the blood urea nitrogen was within normal limits or only slightly elevated. However, the rats which died 24 hours to 72 hours following injection showed marked elevation of blood urea nitrogen. Microscopic examination of their kidneys revealed early granular and hyaline changes in the tubules. Occasional swollen glomeruli were seen, as well as acute congestion. These results suggest that the animals which died of gallium poison within 24 hours did not succumb to a renal death, whereas those surviving for longer than 48 hours showed evidence of moderate renal pathology.

On the basis of these data it may be concluded that the dose of gallium lactate required to kill 50 per cent of rats injected intravenously within 10 days is 46 mg. of gallium per kilogram of body weight (LD 50–10 days equals 46 mg. of gallium per kilogram of body weight).

Gallium lactate was injected subcutaneously into 170 rats. At the range of 20 to 50 mg. of gallium per kilogram of body weight, there was no observable effect other than a transitory loss of weight, and a tendency toward hyperexcitability which lasted for only 24 hours. At levels of 100 to 180 mg. of gallium per kilogram of body weight, the animals showed marked excitability for 24 to 48 hours, then exhibited a characteristic depressed attitude, bordering on semi-coma. However, they remained conscious. Some evidence of photophobia was found which lasted up to 30 days. With the use of these latter dosages, those animals which survived three to five days developed a diarrhea, became emaciated and ate very little food. In many instances, blindness developed two to four days prior to death. Certain of these animals which survived were held for observation up to six months after injection. In these the reduced activity and loss of appetite lasted for 30 or 45 days, after which there was an increase in activity and weight, and at the end of 60 days all of the survivors appeared to be normal. All animals surviving the first 10 days following injection eventually recovered from the effects of the one subcutaneous dose of gallium. Based on the results of these studies, it was therefore concluded that the quantity of gallium used as the lactate required to kill 50 per cent of the rats within 10 days is 121 mg. of gallium per kilogram of body weight. (LD 50, 10 days equals 121 mg. of gallium per kilogram.)

In summarizing the toxic effects of gallium, the following may be concluded:

(1) Rats exposed to aerosols of gallium chloride were affected, but slightly, in concentrations of 0.125 mg. of gallium per liter of air in exposures of one-half to four hours. The acidity of the solutions (pH 2.2) of both gallium chloride and the sodium chloride controls produced the same effects, namely, areas of consolidation in the lungs. It was demonstrated that gallium is deposited in the lungs as the insoluble dihydroxide and does not pass the alveolar membrane.

(2) Rats fed gallium chloride or gallium lactate in doses up to 1,000 parts per million of feed showed no demonstrable effects in periods varying up to 26 weeks. Absorption of gallium salts from the intestinal tract is negligible.

(3) The minimal lethal doses (LD 50) of gallium lactate for rats and rabbits are as follows:

(a) Rats:
1) Intravenous injection, 47 mg. per kilogram of body weight.
2) Subcutaneous injection, 121 mg. per kilogram of body weight.

(b) Rabbits:

1) Intravenous injection, 43 mg. per kilogram of body weight.

2) Subcutaneous injection, 97 mg. per kilogram of body weight.

(4) The symptoms and physical findings resulting from lethal and near lethal injections of gallium salts include:

(a) Loss of weight.
(b) Hyperexcitability.
(c) Photophobia.
(d) Blindness.
(e) Terminal flaccid paralysis.

Early pathologic findings indicate that death may be due to acute respiratory failure. In those animals surviving longer than three to four days some kidney pathology is usually present. In general, animals which survive 10 days following a near-fatal dose of injected gallium recovered apparently wholely within 30 to 45 days.

(5) The dosages in milligrams per kilogram of body weight estimated for use in humans, either for gallium tracer studies or for attempted bone malignancy therapy, are far below the levels required to produce either toxic effects or death in the laboratory animal studies.

IV. Radioactive Gallium

As previously stated, gallium is a rare metal; it has a low melting point (30° C.), and a boiling point of 1,700° C. To date, there is no known commercial use for this rare metal. Gallium has several isotopes. Because of the short half-life (14.3 hours) and the type of radiation emitted, gallium 72 was selected as the ideal isotope of this metal for human application. This isotope has gamma radiation of 2.53 m.e.v., and beta radiation of 2.50 m.e.v. On the basis of favorable results obtained through a long series of animal experiments, it appeared that radioactive gallium might be a favorable isotope for use in humans who have malignancies or other diseases of the bones. With this in mind, the Committee for Application of Radioactive Isotopes in Humans of the U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland, of which the author is chairman, decided to set up a project to study the use of this isotope in patients having advanced malignancies with metastases to bones, both for tracer studies and possibly as therapy for bone pathology. In due time this project was approved by the Atomic Energy Commission, as well as by the nationwide civilian committee. Both of these agencies have reviewed the methodology and procedures of this project. Under their close supervision, it is necessary for the Committee for Application of Radioactive Isotopes in Humans, of the Bethesda Naval Hospital, and the Isotope Laboratory, which works under the direction of this committee, to have authorization for the use of this isotope renewed every six months and to have methods

reviewed at more frequent periodic intervals. Results obtained and progress made must be reported to both of these agencies every six months.

Gallium 72, as used in this study, is produced in the atomic pile at Oak Ridge, Tennessee. Because of its very short half-life (14.3 hours), it is necessary to expedite its shipment and use. It is sent by plane from Oak Ridge to Washington, where it is delivered to the above agencies approximately six hours later. Immediately upon receipt in the Isotope Laboratory of the U. S. Naval Hospital, Bethesda, Maryland, it is calibrated and standardized. For tracer studies, gallium 72 is used within 24 hours of removal from the atomic pile. For use in the studies on therapy of bone lesions, it is used within eight hours of removal from the atomic pile.

Immediately before the administration, each dosage of gallium 72 must be checked to determine accurately the amount of radiation remaining and therefore the proper dosage.

As shown above, after three years of detailed studies on animals it was considered safe for use on humans. Neither the inert gallium nor the radioactive isotopes of gallium seems to enter into the active metabolism of the body.

The plan for diagnostic or tracer studies as now established is to use a tracer dose of 350 to 400 microcuries. For therapeutic use, larger doses are considered necessary. In both uses, radioactive gallium 72 is administered intravenously. It is injected slowly into a sterile tube through which normal saline is being given intravenously to the patient. This is done by means of a lead shielded syringe. Following administration, using Geiger-Müller counters, it was found that 80 per cent of gallium 72 becomes localized within two hours of intravenous injection into humans. In normal bone the localization reaches a maximum within one hour. In the malignancies of bone thus far studied, the maximal localization in the pathologic bone areas is reached within 10 hours.

In all cases studied, the following procedure has been established as standard:

(a) Geiger-Müller counts are taken at one minute intervals for the first two hours.

(b) Additional counts are taken at the third, tenth and twenty-fourth hours after injection. Geiger-Müller counts are taken over a pattern of 40 standard areas of the human body. The interpretation of radiation is based on the rate of counts per minute per designated area of the body. Rates of each area are compared to an average drawn up for all areas.

A detailed description of apparatus used, as well as methodology, is not considered essential to this thesis. Suffice it to state that all apparatus and methods used have been approved by the Atomic Energy Commission, and by the nationwide civilian committee on the human use of radio-isotopes. Furthermore, a constant liaison is being maintained with the U. S. Bureau of Standards, The Carnegie Institute of Washington, George Washington

Medical School, and other activities in the Washington area which work with radioactive isotopes. This also permits a constant review on procedures, methodology and apparatus by those working locally in the field of radioactive isotopes, and keeps these other agencies informed on the progress made at the U. S. Naval Hospital, Bethesda, Maryland.

V. The Use of Radioactive Gallium in Human Malignancies

To date, a total of 12 patients having various types of bone malignancies have been studied by using radioactive gallium 72. These patients were selected primarily from those with proved malignancy and with x-ray evidence of osteoblastic or osteolytic metastases. Following is a list of the types of malignancies studied:

Six patients having carcinoma of the prostate with bone metastases.
Two patients having carcinoma of the breast with bone metastases.
One patient having bronchogenic carcinoma with metastases to bone.
One patient having gastric carcinoma with metastases to bone.
One patient having osteogenic sarcoma with bone metastases.
One patient having osteochondrosarcoma with bone metastases.

It is not considered necessary to present an abstract of each of the 12 patients who have been studied, since results obtained were so closely parallel in a high proportion of these cases.

Following are abstracts of a few of the most typical results, together with the more dissimilar cases:

Case Reports

Case 1. This was a 49 year old male who had carcinoma of the prostate with osteoblastic metastases. He had been treated previously with deep x-ray therapy for over one year and by bilateral orchidectomy and estrogen therapy. This patient had developed progressively increasing bone pain in the right iliac crest, in the lumbosacral joint and in both legs. X-ray films confirmed the presence of metastases in all of these areas. Tracer studies with radioactive gallium revealed an increased pick-up of radiation over the identical metastatic areas that were visible in the x-ray films. The counts over these areas showed a 20-fold increase above those of normal bone in the adjacent areas.

Case 2. This patient was an 82 year old white male who had carcinoma of the prostate with bony metastases. The diagnosis had been established 18 months previous to tracer studies with radioactive gallium. The x-ray films revealed metastases in the second lumbar vertebra with partial collapse. This patient, prior to tracer studies, had been treated by (a) orchidectomy and (b) estrogenic therapy. At the time of the tracer studies the patient had progressively increasing pain in the left hip and in the right pelvis. X-ray films had failed to reveal any evidence of metastases in these latter areas. Radioactive gallium tracer studies revealed a markedly increased deposition of the gallium in the known metastases and in the left hip and right pelvic areas, despite the fact that there were no metastases discernible on x-ray.

Case 3. This patient was a 29 year old white male who had an osteoblastic type of osteogenic sarcoma. The past history elicited a right orchidectomy in 1943.

with subsequent pathologic diagnosis established of carcinoma of the right testis. Following this, he received x-ray treatments of from 2,800 to 4,000 roentgens to each of five ports over a period of two years following the operation. During the year prior to radio-gallium studies, a subcutaneous mass appeared in the midline of the region of the junction of the thoracic and lumbar spine. Recent x-ray films showed trabeculated bone localized in the mass. Pathologic diagnosis established by biopsy of this mass was osteogenic sarcoma. Radioactive gallium tracer studies revealed a 20-fold increase of pick-up over this mass, as indicated by increased Geiger-Müller counts in comparison with the counts of adjacent bony areas.

Case 4. This was a 62 year old white male who had bronchogenic carcinoma with bony metastases. A radical right pneumonectomy had been performed in June, 1949. The pathologic studies confirmed the diagnosis of bronchogenic carcinoma. Two months following operation the patient began to develop aching and pain in the left thigh, and a progressively increasing localized mass gradually appeared in the same area. X-ray films revealed this to be an osteolytic lesion with periosteal elevation of the edges. Radioactive gallium tracer studies revealed a 20-fold increase of Geiger-Müller counts in the area over this metastatic lesion. Also, there were markedly increased counts picked up in the upper lumbar spine, although there was no pain or x-ray evidence as yet of metastases in this area.

Case 5. This was a 55 year old white male patient who had gastric carcinoma with bony metastases. A gastrectomy had been performed three months before tracer studies with radioactive gallium were done. The pathologic studies established the diagnosis of carcinoma of the stomach. Within two months of operation, widespread metastases to the spine were revealed on x-ray bone surveys. The patient had a good clinical response to deep x-ray therapy. One month before tracer studies were begun, metastatic bone pains became progressively worse, and liver enlargement developed which was followed by jaundice. Radioactive gallium tracer studies showed greater than a 20-fold increase of pick-up over all metastatic areas showing on the x-ray films. These studies also indicated the possibility of metastases in the right pelvis and right upper femur, although there was no x-ray evidence of metastases in these areas at the time the radioactive gallium tracer studies were done. Following tracer studies, radioactive gallium was tried as a therapeutic measure in the management of this patient. A therapeutic dose of 1,300 mc. of gallium-72 was injected slowly into sterile tubing through which the patient was receiving normal saline. At the present writing (30 days following this injection), the patient has demonstrated both subjective and objective clinical improvement. His bone pains have decreased, the radicular pain in his upper abdomen has disappeared, and the back pain has become markedly reduced. In addition, his appetite has increased, he has gained slightly in weight, and he feels that he has been benefited by this treatment. He suffered no detectable toxic effects.

Case 6. This was a 60 year old white male who had proved carcinoma of the prostate of 14 months' known duration. Previous treatment had consisted of deep x-ray therapy over both testes and the pelvic bones and diethylstilbestrol therapy, with questionable results. An x-ray bone survey revealed a hypoplastic lesion in the bones of the right pelvis. He complained of progressively increasing pain and tenderness all over the region of the right groin and hip. This was constant and boring in nature. Radioactive gallium tracer studies revealed a greater than 20-fold increase in pick-up over the metastatic area of the right pelvis as revealed by x-ray. No other abnormally high counts were detectable over any other bony areas. It was decided to try radioactive gallium therapeutically in an effort to obtain relief from the severe pain. He was observed for two weeks as an in-patient. At this writing (three months after therapeutic gallium), he has obtained marked relief from pain.

VI. Discussion

It is recognized fully that final and definite conclusions on the value of radioactive gallium in the management of patients with bone malignancies cannot be reached at this time because of the limited number of patients studied thus far. However, the results obtained from radio-gallium studies of the 12 patients indicate strongly that this isotope will ultimately prove to be of value in the management of humans who have neoplasms of bone. Each of the 12 patients on whom these studies were completed had an unmistakable malignancy with bony metastases. In each instance, tracer studies revealed a highly significant increased pick-up of radioactivity over every metastasis demonstrated by x-ray survey of the bones. This was due to the increased deposition of the radioactive gallium in the metastases in excess of that deposited in normal bone. On several occasions, areas of bone were found which emitted increased irradiation after the administration of radioactive gallium and in which no x-ray evidence of metastases could be found. Undoubtedly these were bone areas in which metastases were forming at a stage too early to be demonstrated by x-ray. Only two attempts have been made thus far to treat therapeutically, with radioactive gallium, patients having bone malignancies. Therefore, it is too early to determine with any degree of accuracy the ultimate long-range effect of radioactive gallium on such patients. The meager information derived from the study of these two cases, however, strongly indicates that radioactive gallium at least has a palliative effect in prolonging life and in relieving bone pain and other distressing symptoms.

It is recognized that further studies must be pursued and a large number of cases studied before final conclusions can be drawn regarding the potential value of radioactive gallium in the handling of human patients with bone malignancy. However, the limited studies to date indicate that in the future the use of radioactive gallium will occupy an important place in the armamentarium of hospitals and clinics attempting to treat cancer of the bones.

VII. Conclusions

Studies in the use of radioactive gallium in humans indicate:

(1) There is complete agreement with the results of animal experimentation.

(2) There is no evidence of toxicity or any untoward effects in the doses used in humans.

(3) As to localization of radioactive gallium in humans:

(a) It has the same pattern of localization in humans as in animal experiments.

(b) Geiger-Müller counts taken over the kidneys in humans showed up to an increase of eight-fold over the average for the entire body.

(c) The liver pick-up in humans increased two- to three-fold over the average for the entire body.

(d) The bone pick-up in humans was more than 10-fold above the average for the entire body.

(e) Primary and secondary malignancies of the bone showed a concentration of counts of over 20-fold greater than the average for the entire body with clean cut localization, using a shielded Geiger-Müller tube.

(4) Toxicity studies, as determined by careful animal experiments, show that the dosage levels required for radioactive gallium used in humans are well below the danger zone.

(5) Physiologic distribution, localization, concentration and excretion of gallium 72 in humans are identically the same as those in animals.

(6) Radioactive gallium will localize in either primary or secondary bone tumors, in either osteoblastic or osteolytic lesions.

(7) It can be expected from the studies on humans that diagnoses of early bone malignancies may be made by this method before the appearance of pain or x-ray evidence of such metastases.

(8) The concentration of radioactive gallium in human bone lesions is 20-fold greater than in normal bone.

(9) Radioactive gallium shows indication of being a palliative form of therapy for the treatment of malignancies of the bone.

(10) The short-life of radioactive gallium 72 makes control of the radiation dosage much easier and reduces the possibility of prolonged harmful residual radiation effects.

(11) Because of its selective location in desired bony structures, these therapeutic advantages over other materials warrant further investigation.

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A QUANTITATIVE EVALUATION OF THE CONTRIBUTION OF NITROGEN MUSTARD TO THE THERAPEUTIC MANAGEMENT OF HODGKIN'S DISEASE *

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THE nitrogen mustard, methyl bis (beta chloroethyl) amine (HN_2), was introduced as a chemotherapeutic agent in the treatment of malignant disease in 1943 by Goodman et al.[1] Since that time there have been over 50 reports in the American literature describing the immediate effects of nitrogen mustard on a variety of neoplastic processes. Although there has been excellent agreement on the qualitative responses observed in the various clinics, there is but one report which assesses quantitatively the contribution of HN_2 in the medical management of certain malignant diseases.[2] Since HN_2 is now commercially available to the medical profession under the trade name of Mechlorethamine,† it would appear profitable to evaluate as precisely as possible the results of nitrogen mustard therapy observed in a series of patients followed for an adequate period of time as a guide to the indications and limitations of this form of treatment.

The clinical reports are unanimous in stating that the most dramatic responses of HN_2 are seen in patients with Hodgkin's disease. In the past, the conventional treatment of this disease has been by irradiation of involved sites. The natural course of Hodgkin's disease treated by roentgen-ray is characterized by prolonged symptom-free remissions following effective therapy to localized areas of involvement. However, as the manifestations of disease become more widespread, more fields must be irradiated, the remission intervals are shorter, and eventually the malignant process is said to be "radio-resistant" and therapy is ineffective. In spite of the fact that reported clinical studies have demonstrated that remissions can be induced by nitrogen mustard in Hodgkin's disease even when patients are preterminal, the following questions remain unanswered: (a) At what stage in the course of Hodgkin's disease should HN_2 be introduced into the therapeutic regimen? (b) Does the appropriate use of HN_2 significantly prolong the lives of patients with Hodgkin's disease? (c) Does the use of HN_2 decrease the amount of irradiation necessary? The present report will provide quantitative information obtained during the past four years which bears on these issues.

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† Merck and Co., Rahway, N. J.

MATERIAL

The results to be reported in this paper are on 67 patients with Hodgkin's disease who have been followed from six months to four years on a therapeutic regimen of roentgen-ray therapy and nitrogen mustard in alternating courses. When this investigative program was initiated four years ago, it was decided to determine whether the alternation of the two forms of treatment in Hodgkin's disease might prevent the development of refractoriness to either therapeutic method and thereby prolong life. Since, however, it had been clearly demonstrated that nitrogen mustard was not a curative agent, the drug was withheld from all patients in whom the manifestations of the disease were localized to one area or even one region. Thus, for example, a patient with unilateral cervical lymph node enlargement and roentgen evidence of hilar adenopathy received radiotherapy only. The criteria for "generalized" disease included generalized lymphadenopathy and evidence of visceral involvement; constitutional symptoms of fever or diffuse pruritus and osseous involvement along with one other site of evident disease. When a patient showed these evidences of disseminated disease, he became a candidate for inclusion in the study and might receive radiotherapy or nitrogen mustard as the initial form of treatment. At the outset of the program, alternate patients received roentgen-ray or nitrogen mustard as the initial method of treatment. However, as our experience increased, it appeared more satisfactory to administer nitrogen mustard first and then to treat any residual evidences of disease with roentgen-ray, if necessary. Whether patients received radiotherapy or chemotherapy at the outset, the two forms of treatment were thereafter alternated unless specific contraindications arose or unless it was clear that one method of treatment was ineffective. All patients in this series were closely followed in a special clinic, and the indications for giving treatment were based on clinical evidence of symptomatic disease.

The results of "combined" treatment of these 67 patients with Hodgkin's disease using nitrogen mustard and roentgen-ray therapy have been compared with 65 consecutive cases of this disease treated by radiotherapy alone prior to 1946. It is the comparison of the results in these two series of patients upon which our conclusions rest.

Little discussion of the nitrogen mustard regimen is necessary because of the many detailed descriptions in the literature. We explored a variety of dosage schedules and found that, for the majority of the patients, 0.2 mg. per kilogram of body weight on two successive days was the most satisfactory. Heavy preinjection medication with barbiturates was a part of the routine, to reduce the unpleasant immediate toxic manifestations of nausea and vomiting.

Radiotherapy was carried out with 180, 200 or 250 KV (HVL 0.9–1.5 mc.). Earlier patients were treated to regression of evident disease or

symptomatic improvement with a dose in air varying from 500r to 2,500r. A few cases received prophylactic radiation to mediastinum or retroperitoneal regions. More recently the treatment policy has been to deliver radiation representing about 70 per cent of the tolerance dose to the involved site when the disease was localized, or 50 per cent of the tolerance dose to the involved site when the disease was generalized. This statement is intended to take into account the time, dose, and volume relationship.

Results and Discussion

The results of this clinical investigation have been analyzed from several standpoints to bring out pertinent facts about both the therapeutic regimens under consideration and the course of Hodgkin's disease.

Table I

Analysis of Survival Rates from Diagnosis in Patients with Hodgkin's Disease Treated by Radiation and Nitrogen Mustard or Radiation Alone

	(1) Years after diagnosis	(2) Number present at beginning of year	(3) Number living last observed between x & x+1	(4) Number dying between x & x+1	(5) Number lost to follow-up between x & x+1	(6) Effective number present during year	(7) Probability of dying during year	(8) Annual survival rate (%)	(9) 4 year survival rate (%)	(10) 4 year death rate (%)
	x	l_x	w_x	d_x	lo_x	$l_x-\frac{1}{2}w_x+\frac{1}{2}lo_x$	q_x			
A Radiation and Nitrogen Mustard	0	67	5	16	3	63	0.25	75		
	1	43	6	4	0	40	0.10	90		
	2	33	6	7	1	29.5	0.24	76	48.2	51.8
	3	19	3	1	0	17.5	0.26	94		
	4	15	3	3	0	13.5	0.22	78		
	5–9	9	4	3	1					
	10+	1	1	0	0					
B Radiation Alone	0	65	0	14	2	64	0.22	78		
	1	49	2	6	2	47	0.13	87		
	2	39	1	4	1	38	0.10	90	47.6	52.4
	3	33	1	7	1	32	0.22	78		
	4	24	0	4	0	24	0.17	83		
	5–9	20	7	6	2	15.5	0.39	61		
	10+	5	4	1	0					

In table 1 there is presented a summary of survival rates in Hodgkin's disease in the two series of patients previously described from the time of definitive diagnosis by biopsy. In these data, as in the remainder of the data to be summarized, there are three categories of cases to be integrated: patients who have died, patients who are still living after variable periods of observation, and patients who were lost to follow-up after variable periods of observation. A standard actuarial technic has been employed in this analysis which will be briefly described.

The basic data are given in columns 1, 2, 3, 4 and 5; the remaining columns are computations. To illustrate the method, the values of part A

in table 1 will be discussed from left to right. In column 1, the 0 refers to the time interval from the time of diagnosis through the first year after diagnosis. In column 2, the 67 refers to the total number of cases in the series; they were selected throughout a long time period but they are all grouped together from diagnosis at time 0. In column 3, the number living recorded as 5 refers to patients who were under observation for a period of less than one year from the time of diagnosis; in column 4, the number of patients who died (16) in the first year after diagnosis is given, and column 5 shows that three patients were lost to follow-up during the first year after diagnosis. This latter group is an unknown; it is possible that they are all dead or all alive, or divided between living and dead. In any evaluation of survival statistics, this group of "lost to follow-up" introduces an error the magnitude of which is determined by the size of the group in relation to the total number of cases under study. Fortunately, in the present analysis the number of patients "lost" is small. Arbitrarily, it has been decided to incorporate the patients listed in column 5 with those of column 3 for computation purposes. This is permissible because the comparative results would in no wise be altered if all of these patients were arbitrarily considered to be dead. Thus, in the first year there are eight patients ($w_x + lo_x$) who have been followed for less than one year. These eight patients have been exposed to the risk of dying for various periods of less than an entire year, and appropriate correction must be made for this fact in computing the probability of dying. This is done by assuming that, on the average, these eight patients were observed for six months of the year or, for purposes of calculation, that one-half of this group was exposed to the risk of dying during the entire year. Column 6, the effective number of patients present during the year, incorporates this correction. Thus, in the first year after diagnosis, although there were a total of 67 cases, one-half of $5 + 3$ must be subtracted, since they were not exposed to the risk of dying during the entire year. In column 7, then, the probability of dying is computed from

$$\frac{\text{Number dying during year (column 4)}}{\text{Effective number present during year (column 6)}}$$

or $16/63 = 0.25$. The annual survival rate is the reciprocal of this value times 100.

In the next year, there are no longer 67 cases for analysis, because there have been withdrawals from the series due to death, due to too brief follow-up, and due to loss to follow-up. Thus the total number present at the beginning of the second year (column 2) now is $67–5–16–3 = 43$. The procedures described above are duplicated throughout the table. The four-year survival rate is calculated by multiplying the annual survival rates serially, and the four-year death rate is the reciprocal of the four-year survival rate.

As can be seen from table 1, the four-year survival rate from the time of diagnosis is not significantly different in patients who received nitrogen mustard and radiation and in those who received radiotherapy alone. Our analyses have been made on the basis of a four-year interval rather than five years because, after four years in the "Radiation and Nitrogen Mustard" group, the number of cases available for analysis is so small that the validity of the calculations is questionable. However, to obtain a rough estimate of the five-year survival rate, the figure for four years can be multiplied by

TABLE II

Analysis of Survival Rates from Onset of Symptoms in Patients with Hodgkin's Disease Treated by Radiation and Nitrogen Mustard or by Radiation Alone

	Years after onset of symptoms	Number present at beginning of year	Number living last observed between x & x+1	Number dying between x & x+1	Number lost to follow-up between x & x+1	Effective number present during year	Probability of dying during year	Annual survival rate (%)	4 year survival rate (%)	4 year death rate (%)
	x	l_x	w_x	d_x	lo_x	$l_x - \frac{1}{2}w_x + lo_x$	q_x			
A Radiation and Nitrogen Mustard	0	67	3	11	0	65.5	0.17	83	52.3	47.7
	1	53	3	8	2	50.5	0.16	84		
	2	40	3	3	2	37.5	0.08	92		
	3	32	7	5	0	28.5	0.18	82		
	4	20	2	4	0	19	0.20	80		
	5	14	3	0	1	12	0.00	100		
	6	18	1	0	0	9.5	0.00	100		
	7	9	2	0	0	8	0.00	78		
	8	7	0	2	0	7	0.28	100		
	9	5	0	0	0	5	0.00	25		
	10 or more	5	2	3	0	4	0.75			
B Radiation Alone	0	64	0	5	1	63.5	0.08	92	54.8	45.2
	1	58	1	9	3	56	0.16	84		
	2	45	1	4	0	44.5	0.09	91		
	3	40	1	8	1	39	0.21	79		
	4	30	0	3	0	30	0.10	90		
	5	27	1	5	1	26	0.19	81		
	6	20	1	1	0	19.5	0.05	95		
	7	18	2	4	1	16.5	0.25	75		
	8	11	0	0	0	11	0.00	100		
	9	11	3	1	1	9	0.11	89		
	10 or more	6	5	1	0	3.5	0.29	71		

the survival rate of the fifth year after diagnosis: $48.2 \times 78 = 37.6$ per cent for the combined treatment group, and $47.6 \times 83 = 39.5$ per cent for the radiotherapy alone series.

In table 2, analyzed in the same manner as described for table 1, the survival rates in the two series of patients were determined from the onset of symptoms. Here the patients' subjective evaluation introduces a possible error. However, it is interesting to note that the survival rates are not significantly greater than those obtained when definitive diagnosis is made the starting point of the observations. It is also to be pointed out

that the survival rate of patients treated by radiation and nitrogen mustard is not significantly different from that of patients receiving radiotherapy alone.

Since all of the patients receiving nitrogen mustard had evident generalized disease as a condition of their receiving chemotherapy, it was considered of interest to determine the survival rates in the two series of patients after the onset of objective disseminated Hodgkin's disease. This analysis is summarized in table 3. As can be seen, the combination of nitrogen mustard and radiotherapy was followed by a four-year survival rate of 43.5 per cent in patients with generalized disease, whereas the comparable

TABLE III

Analysis of Survival Rates in Patients Treated by Radiation and Nitrogen Mustard or by Radiation Alone from Evident Generalization of Disease

	Years after generalization of disease	Number present at beginning of year	Number living last observed between x & x+1	Number dying between x & x+1	Number lost to follow-up between x & x+1	Effective number present during year	Probability of dying during year	Annual survival rate (%)	4 year survival rate (%)	4 year death rate (%)
	x	l_x	w_x	d_x	lo_x	$l_x-\frac{1}{2}w_x+lo_x$	q_x			
A Radiation and Nitrogen Mustard	0	67	6	15	3	62.5	0.24	76	43.5	56.5
	1	43	4	8	1	40.5	0.20	80		
	2	30	7	6	1	26	0.23	77		
	3	16	4	1	0	14	0.07	93		
	4	11	1	2	0	10.5	0.19	81		
	5–9	8	4	2	0	6	0.33	67		
	10 or more	2	1	1	0	1.5				
B Radiation Alone	0	56	0	17	5	53.5	0.32	68	34.3	65.7
	1	34	1	7	0	33.5	0.21	79		
	2	26	0	4	1	25.5	0.16	84		
	3	21	0	5	0	21	0.24	76		
	4	16	1	3	0	15.5				
	5–9	12	5	4	2	8.5	0.47	53		
	10 or more	1	0	1	0	1				

value in patients receiving radiotherapy alone was 34.3 per cent. This apparent difference, however, is not statistically significant and could occur by chance alone. Therefore, on the basis of available evidence, it must be concluded that nitrogen mustard given to patients with generalized Hodgkin's disease in alternation with radiotherapy does not prolong life to a greater extent than when radiotherapy is the sole definitive therapeutic regimen.

The 132 patients who make up the two series of cases treated by radiation alone and by radiation and nitrogen mustard were followed at frequent intervals, and when evident or symptomatic disease was found treatment was given. For this reason it was of interest to compare the number of radiation treatment-days in the two series to determine whether the use of nitrogen

mustard had appreciably decreased the necessity for radiotherapy. The results of this survey are summarized in table 4. As can be seen, on the average, patients on radiotherapy alone received roentgen-ray treatments for seven and one-half days per month, whereas only three and six-tenths days of radiation per month for patients on combined therapy were necessary. Statistical analysis of these two averages shows that the difference would not be expected to occur by chance alone, and therefore the difference is considered significant. These figures by strict interpretation show that the amount of time devoted to radiotherapy is cut in half when radiation and nitrogen mustard are used in the management of Hodgkin's disease, as

TABLE IV

Number of Radiation Treatment-days per Month in Patients with Hodgkin's Disease Receiving Radiotherapy Alone and in Patients Receiving Radiotherapy and Nitrogen Mustard

Radiation Treatment-days per Month	Number of Patients	
	Radiotherapy Alone	Radiotherapy and Nitrogen Mustard
0– 1.9	17	30
2– 3.9	10	16
4– 5.9	6	11
6– 7.9	8	3
8– 9.9	6	2
10–11.9	3	3
12–13.9	5	0
14–15.9	1	0
16–17.9	3	1
18–19.9	1	0
20–21.9	4	1
22–23.9	0	0
24–25.9	1	0
Total	65	67
Average Radiation Treatment-days per Month	7.4	3.6

compared with the duration of radiation when radiotherapy is the sole therapeutic procedure. By implication, however, this analysis indicates more: (1) The total amount of radiation required by patients on the combined therapeutic regimen is probably less. (2) Since in the two series therapy was given when symptoms were present, and since symptomatic relief following the administration of nitrogen mustard is rapid, these figures suggest that patients receiving chemotherapy and radiotherapy were asymptomatic for a longer period during the course of their disease than the other group of patients. (3) Finally, again only by implication, the economic burden of the disease was decreased by the combination therapy, inasmuch as the majority of the nitrogen mustard treatments were given on an ambulatory basis and the total cost of radiotherapy was decreased because the number of visits required was reduced.

An analysis devoted solely to the experience with nitrogen mustard in this series of patients revealed certain points of practical importance. One hundred forty-four courses of nitrogen mustard have been given to the 67

patients in the series reported. Significant toxicity occurred following 10 courses of chemotherapy, an incidence of 7 per cent. Significant toxicity, which was limited to depression of hematopoietic function in every instance except one, was defined as leukopenia of 1,000 or less, thrombocytopenia of 70,000 or less, or hemorrhagic manifestations regardless of the platelet count. No overwhelming pyogenic infections occurred in any of the patients who developed leukopenia; however, antibiotics were of course employed prophylactically. The hemorrhagic complications, with or without thrombopenia, were limited to subcutaneous bleeding and oozing from the gums. No serious involvement of the gastrointestinal tract, other viscera, the central nervous system or serous cavities was associated with the purpura. In the entire series of patients there was only one death in which nitrogen mustard was believed a probable contributing factor. Because the complication of the chemotherapy was unexpected, and because we feel that the experience demonstrates a specific contraindication to nitrogen mustard therapy, a brief report will be included here.

Case Report

A 48 year old Negro male bellboy captain had a five-month history of low back pain, weakness, anorexia, 25-pound weight loss, enlargement of cervical nodes and pain in the left leg. In 1942 the patient was rejected by the army because of a pulmonary lesion. Repeated roentgenographic examinations of the chest from 1942 to 1948 by the Board of Health led to the diagnosis of "tuberculosis, inactive." At time of admission to the Presbyterian Hospital the patient was acutely ill, with temperature from 102° to 104° F. There were generalized lymphadenopathy, massive in the cervical region, hepatosplenomegaly and neurologic evidence of involvement of peripheral nerves to the left leg. A skeletal survey was negative. Chest roentgenogram revealed hilar adenopathy and marked pleural thickening over the right apex, together with shadows consistent with pulmonary infiltration of the right upper lobe. Hemoglobin was 6.0 gm.; red blood cells, 2.55 million; white blood cells, 2,280; platelets, 124,000; erythrocyte sedimentation rate, 119 mm. in 1 hour; sputum culture: *Streptococcus viridans*; spinal fluid chemistry, normal, culture negative. Biopsy of cervical lymph node revealed Hodgkin's disease, granuloma type. Patient received nitrogen mustard, 0.2 mg. per kg. × 2. There was a rapid decrease in size of the peripheral lymph nodes noted two days after completion of the treatment, but no significant change in the hepatosplenomegaly. There was progressive pancytopenia. On the ninth day after mustard, red blood cells were 2.9; hemoglobin, 6.9; white blood cells, 1,000; platelets, 42,000. On the tenth day the patient had involuntary tremors of the upper extremities and had episodes of disorientation. There were no neurologic findings suggestive of meningitis. A chest roentgen-ray revealed fine mottled infiltration throughout both lung fields consistent with the appearance of miliary tuberculosis. The patient's course was steadily downward in spite of streptomycin therapy, and he died 20 days after the completion of the nitrogen mustard injections. At necropsy, unequivocal evidence of Hodgkin's disease was found in many of the lymph nodes and in the spleen—small foci consisting of a few lymphocytes, large mononuclear cells and very rarely a Reed-Sternberg cell embedded in a dense, pale pink staining collagenous matrix. In view of the dense and ubiquitous cellularity of the original lymph nodes, the fibrosis was presumably the result of the nitrogen mustard therapy. Intermixed with the Hodgkin's infiltrates was a miliary caseous

tuberculosis. Tubercles were also found in the liver, prostate, lungs and bone marrow. In the apex of the upper lobe of the right lung there was an area of fibrocaseous tuberculosis. The pathologist did not feel that a categorical answer could be given to the question of whether the nitrogen mustard had activated the lesion. However, the extensive caseation of most of the lesions, indicating the abrupt discharge of a large number of organisms into the blood stream, suggests the sudden dissolution of cellular defense barriers.

Comment: In the series of patients with Hodgkin's disease treated with nitrogen mustard there have been two other patients with "inactive" tuberculosis. In neither of these patients was there any evidence of immediate activation of the infection following treatment. One of these two patients died 18 months after nitrogen mustard therapy with tuberculous meningitis. In this patient it is extremely difficult to relate death to the nitrogen mustard therapy; however, it must be recognized that the coincidence of tuberculosis and Hodgkin's disease may increase the hazard of nitrogen mustard therapy, and therefore constitutes a contraindication to this form of treatment.

Objective and subjective remissions following the 144 courses of therapy occurred in 113 instances or, in other words, immediate benefit followed 78 per cent of the treatment courses given. This is a qualitative appraisal and provides no insight into the duration of the remissions induced. A survey of the remission intervals following nitrogen mustard and after radiotherapy has been made. Our reaction to the data assembled was that they were meaningless. Since both radiation and nitrogen mustard are palliative therapeutic measures, a remission interval cannot be precisely defined. Further, in the group of patients receiving both radiotherapy and chemotherapy, the attempt was made to determine how best to use the available forms of treatment. Thus, for example, an individual with marked temperature elevation and other constitutional symptoms who also had a large cervical mass would receive nitrogen mustard on an ambulatory basis. Usually within a week such a patient would experience marked subjective relief, but the cervical adenopathy might be only partially reduced. Radiotherapy to the residual evident disease would then be initiated. Obviously, remission intervals in such a case would be very artificial, since no attempt would be made to withhold radiation until it was absolutely required.

Summary and Conclusions

A critical evaluation of the contribution of nitrogen mustard in the therapeutic management of Hodgkin's disease has been made. The course of the disease has been compared in two groups of patients: 67 cases who received radiation and nitrogen mustard in alternating therapeutic courses as indicated, and 65 cases who received radiotherapy alone. The available evidence shows that the four-year survival rate from the onset of symptoms, from the time of biopsy diagnosis, or from the time of evident generalized disease is not significantly different in the two groups of patients. It is

concluded, therefore, that the addition of nitrogen mustard to the therapeutic regimen of radiation does not modify the duration or life expectancy of the disease.

Evidence has also been accumulated which demonstrates that the amount of time necessary for radiation treatments is reduced by one-half in the patients receiving radiation and nitrogen mustard when compared to the radiation treatment-days of patients receiving radiotherapy alone. This suggests that the amount of radiation required is less, the asymptomatic period greater and the economic burden lighter for the patients on the former therapeutic regimen than on the latter.

The incidence of serious toxicity in the 144 courses of nitrogen mustard given to the 67 patients was 7 per cent. One death occurred in a patient due to a miliary dissemination of pulmonary tuberculosis following the administration of nitrogen mustard.

Immediate subjective and objective improvement followed 78 per cent of the courses of nitrogen mustard.

It is concluded that nitrogen mustard is a useful adjunct to radiotherapy in the management of Hodgkin's disease in that it reduces the requirements for radiation; however, life is not prolonged by the addition of chemotherapy to the conventional therapeutic regimen for Hodgkin's disease.

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EXTRATHYROIDAL HYPERMETABOLISM: CLASSIFICATION AND DISCUSSION INCLUDING THREE ILLUSTRATIVE CASE REPORTS *

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THE problem presented by patients with elevated basal metabolic rates in whom careful study precludes a diagnosis of hyperthyroidism is exceedingly complex. Since the basal metabolism as measured is the sum of the rates of oxygen consumption of all the cells of the body (which number about 40 quintillion), and these in turn are controlled by physical, humoral, endocrine, pharmacologic and vegetative as well as central neural factors, the complexity is expected and understandable. Table 1 illustrates the many clinical, physiologic and physical factors the clinician must keep in mind when confronted with this problem.

I. DISORDERS OF THE ENDOCRINE SYSTEM

A. *Pituitary Gland:* Hypophyseal effects on oxygen consumption are of two types: the first is a thyroidal effect due to thyrotropic hormone, and the second is due to a factor or factors the chemistry of which is unknown.

One might presume that when a patient with acromegaly shows an elevated metabolic rate, the effect is due solely to an increased production of thyrotropic hormone by the anterior pituitary gland with consequent thyroidal hyperplasia. In favor of this hypothesis, Cushing and Davidoff [1] found that 25 per cent of 72 patients with acromegaly had palpable goiters. Of the group, 32 patients had basal rates over + 10 per cent, with an average of + 26 per cent, and only six had rates below — 10 per cent. However, against a purely thyrotropic mechanism for the hypermetabolism was the fact that the majority of the goiters were colloid in type. The histologic picture was unlike that found in toxic diffuse goiter; moreover, it was uncommon for either the goiter or the elevated metabolic rate to respond to a therapeutic trial with Lugol's solution. One patient with acromegaly and a basal metabolic rate of + 60 per cent underwent a subtotal thyroidectomy, following which her basal rate only fell to + 30 per cent. Her goiter proved to be colloid in type. Boothby and Sandiford [2] reported 30 cases of acromegaly in which 15 had basal metabolic rates above + 10 per cent and 13 had rates within normal limits.

Although acromegaly exhibits hypermetabolism which is at least partially extrathyroidal, the mechanism is obscure. O'Donovan [3] noted that

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TABLE I

Clinical, Physiologic and Physical Factors Producing Extrathyroidal Hypermetabolism

I. Disorders of the Endocrine System
  A. Pituitary Gland
    1. Acromegaly
    2. Basophilic adenoma
  B. Adrenal Gland
    1. Medullary tumors (pheochromocytoma)
    2. Cortical tumors
II. Disorders of the Hematopoietic System
  A. Anemia
  B. Polycythemia
  C. Leukemia
III. Disorders of the Collagen System
  A. Dermatomyositis
  B. Disseminated lupus erythematosus
IV. Disorders of the Circulation
  A. Congestive failure
  B. Essential hypertension (?)
  C. Aortic stenosis
  D. Arteriovenous aneurysm
V. Neoplastic Disorders
  A. Malignant tumors with and without metastases
  B. Multiple myeloma
  C. Hodgkin's disease
  D. Lymphosarcoma
VI. Disorders of the Skin
  A. Diffuse erythrodermas
VII. Disorders of the Nervous System
  A. Hypothalamic disturbances
  B. Cortical disturbances
  C. Motor disturbances
VIII. Disorders of the Osseous System
  A. Paget's disease of bone
IX. Hemochromatosis
X. Drugs
  A. Thyroid (thyrotoxicosis factitia)
  B. Thyroxine
  C. Epinephrine
  D. Ephedrine
  E. Caffeine
  F. Histamine
  G. Dinitrophenol
  H. Theophylline-ethylenediamine (aminophylline)
XI. Pregnancy
XII. Fever
  A. Infections
  B. Drugs (tetrahydronaphthylamine)
XIII. Technical Errors
  A. Oxygen loss
    1. Mechanical
    2. Perforated ear drums
    3. Aerophagia
  B. Forced hyperventilation
  C. Voluntary alterations in chest capacity
  D. Discomfort of patient
    1. Salivation
    2. Pain

the injection of pituitary extracts in rabbits produced a transient rise in metabolic rate to + 40 per cent. Riddle and his co-workers [4] demonstrated a similar factor in pituitary extracts believed to be prolactin, which induced hypermetabolism in the pigeon. The active factor in these anterior hypo-

physeal extracts was not thyrotropic hormone, because the action could be demonstrated in thyroidectomized animals; moreover, there was no lag period following the injection, as with thyroid hormone. The effective dosage of the factor was small enough to preclude explaining the effect on the basis of specific dynamic action, and there was no reason to believe such extracts contained epinephrine or any substance of a like nature known to increase oxygen consumption. It is certainly possible that these extracts may contain a principle which explains, at least in part, the hypermetabolism of acromegaly. It is possible that such a factor might be responsible for the elevated metabolic rates of the several patients described by Man and Peters [5] who exhibited hyperlipemia and diabetes. The hypermetabolism responded neither to thyroidectomy nor to a therapeutic dose of iodine.

Cases of basophilic adenoma of the pituitary gland exhibiting the clinical features of Cushing's syndrome are rare. Therefore, it is difficult to evaluate the few cases with hypermetabolism described by Cushing.[6, 7]

B. *Adrenal Gland:* The hypermetabolism of patients with pheochromocytoma is well known [8-12] and the explanation for the phenomenon reasonably clear. Boothby and Sandiford [13] demonstrated prompt elevation of the basal metabolism following small subcutaneous doses of epinephrine. Intravenous epinephrine, in dosage of 0.05 gamma per kilo per minute, caused an elevation of metabolic rate of 8 to 17 per cent in man.[14] Blumgart [15] noted an increase of 16 per cent in the basal metabolic rate of six normal subjects following the subcutaneous injection of average doses. Starr and his co-workers [16] administered subcutaneously 0.45 to 1.0 mg. of epinephrine to six patients; heat production increased in each with an average of 30.4 per cent.

While a part of this calorigenic effect might be due to central nervous system stimulation, with its attendant increase in general skeletal muscular tone, enough in vitro effects of epinephrine have been observed to secure for the substance a rôle in metabolism at a cellular level. Abderhalden and Gellhorn [17] showed that epinephrine in dilutions of $1:5 \times 10^4$ caused increased respiration of cardiac and skeletal muscle, liver and stomach. Ahlgren,[18] working with minced frog muscle, demonstrated increased oxygen consumption at dilutions of epinephrine of $1:10^7$, while at higher concentrations respiration was depressed.

Part of the calorigenic effect may also be due to the work of the heart, since experiments with heart-lung preparations have shown rough proportionality between the increase in cardiac rate and the total gaseous exchange.[19] The calorigenic response to epinephrine is apparently complex; in animals maintained on carbohydrate-free diets, the effect failed to appear.[20] In thyroidectomized animals, the effect was diminished or absent.[21, 22] This latter fact does not imply that the action of epinephrine is indirectly thyroidal, since the prompt calorigenic response of epinephrine is totally unlike the delayed response to thyroxine. There is also some question as to whether

the liver is necessary for this calorigenic action.[23] It has been demonstrated that large doses of vitamin A depress the calorigenic response to epinephrine.[24] It is apparent that the increased oxygen consumption following epinephrine depends on many factors, and thus it is easily understandable why at times a patient with pheochromocytoma may not exhibit hypermetabolism.

The adrenal cortex is probably not responsible for clinical hypermetabolism. Those few cases of Cushing's syndrome with elevated basal metabolic rates may well be explained on the basis of increased thyrotropic hormone. In fact, crude adrenocortical hormone appears to lower the metabolic rate in vivo.[25, 26, 27]

II. Disorders of the Hematopoietic System

Extrathyroidal hypermetabolism is found in anemia, polycythemia and leukemia.

In anemia, the elevation is as a rule moderate,[2] while the metabolic rate in pernicious anemia is in general somewhat higher than in the normochromic or hypochromic varieties.[28] Three factors must be evaluated in the hypermetabolism of anemia. The presence of cardiac decompensation, as will be discussed later, may contribute to the elevated rate. Rapid oxygen consumption of metabolically active stem cells may be invoked as an explanation. However, when patients with pernicious anemia exhibiting hypermetabolism were treated with liver and developed a reticulocyte response, the metabolic rate decreased rather than increased, as one would expect from such a mechanism.[28] Lastly, it is possible that a disturbed nitrogen metabolism caused by anemia might produce an endogenous specific dynamic effect.

Bliss [29] noted that 15 of 23 cases with polycythemia vera exhibited a metabolic rate of more than + 10 per cent. Values were usually moderate, though rates of + 50 per cent were seen. Several explanations have been offered to account for the hypermetabolism. An increased number of metabolically active young cells is certainly present and should account for at least some of the effect.[30] The question of endogenous specific dynamic effect from nuclear material represents a distinct possibility.[31] It must be kept in mind that many of these patients are in various degrees of cardiac decompensation due to increased demand on the myocardium. They may manifest thrombotic phenomena in the coronary arteries and hypertension.

In leukemia, hypermetabolism is the rule. Riddle and Sturgis [32] studied 36 cases of chronic myelogenous leukemia, and in every untreated case the metabolic rate was above + 10 per cent. In fact, these workers found that the metabolic rate was a fair index of the response to therapy, since a rapid fall to normal levels frequently followed a course of irradiation. The cause of the hypermetabolism is again speculative. Certainly, one factor is the high intrinsic metabolic rate of immature cells. Baldridge and Barer [33] believed that the increased protein catabolism might play a rôle. Some of

their patients with leukemia exhibited negative nitrogen balance to the extent of 20 gm. a day. However, mere negative nitrogen balance does not as a rule lead to hypermetabolism; as a matter of fact, starvation depresses oxygen consumption. A fundamental difference exists in the efficiency of work in the hypermetabolism of leukemia and that of hyperthyroidism. Hyperthyroidism, unlike leukemia, is associated with considerable loss in the efficiency of muscular work.[34]

III. Disorders of the Collagen System

Dermatomyositis with hypermetabolism was reported by Joachim[35] in 1923. This was a case of a 37 year old male with joint swellings, muscle stiffness, skin lesions and gastric complaints. His metabolic rate was + 25 per cent, with a pulse rate of 124. Another case, reported by Carney,[36] was a 24 year old male with a metabolic rate of + 28 per cent. Although lupus erythematosus is not usually accompanied by hypermetabolism not explainable by fever, one case (afebrile) of disseminated lupus with hypermetabolism was described by Reifenstein et al.[37] The explanation of the hypermetabolism is not clear.

In a case of dermatomyositis presented below, the evidence for the extrathyroidal origin of the hypermetabolism on the basis of radioiodine studies is quite convincing. It is probable that the abnormal protein metabolism produced considerable muscle spasm; it is believed, however, that the metabolic rate in this patient was too high to be explained entirely on this basis.

Case 1. A 47 year old Italian-born male clothes presser was admitted to the hospital with complaints of joint pains and generalized weakness.

History of Present Illness: The arthritis began about 25 years ago with swelling and erythema of the right shoulder. The disease progressed through the intervening years, with involvement of the hands, knees, ankles, spine and wrists. However, he was able to work at his occupation until quite recently, when he noted weakness, anorexia, impotency and weight loss. Two months prior to admission a positive blood Wassermann was obtained, although there was no history of a chancre. Twenty injections of penicillin were given.

Past, Personal and Family Histories: These were noncontributory.

Physical Examination: The patient was a thin, emaciated, chronically ill male with marked joint deformities. The head and neck were not remarkable except for xanthelasma. The liver and spleen were not palpable. The genitalia and rectum were negative. A few axillary and inguinal nodes were felt. Heberden's nodes were present. Exostoses of the elbows, wrists and ankles were noted.

Laboratory Examinations: The basal metabolic rates varied from 39 per cent to 67 per cent above the average normal on eight separate occasions; the blood count showed a mild secondary anemia, with a total white cell count of 9,300, with 41 per cent polymorphonuclear neutrophils, 3 per cent eosinophils, 48 per cent lymphocytes and 8 per cent monocytes; urinalysis was normal; blood chemistry revealed the absence of nitrogen retention and normal serum calcium, alkaline phosphatase and whole blood chlorides; serum cholesterol, 150 mg. per cent, total serum proteins, 8.5 gm. per cent; serum albumin, 4.3 gm. per cent; globulin, 4.2 gm. per cent, and sedimentation rates which varied from 117 to 124 mm./hour; glucose and galactose

tolerance tests were normal; spinal fluid examination revealed nothing abnormal; the urinary 17-ketosteroids were 9.1 mg./24 hours; the Kepler-Robinson water test was positive in both Parts I and II, the latter being 6.1; urinary creatine excretions were markedly increased, ranging from 1,200 to 2,056 mg./24 hours; liver function tests revealed no bromsulfalein retention; cephalin-cholesterol flocculation, 4 plus; thymol turbidity, 7.5 units; thymol flocculation, 4 plus, and colloidal red, 5 units; blood serology was negative; the serum sodium varied from 123 to 144 m.Eq./L., and the serum potassium from 5.4 to 7.4 m.Eq./L.; the serum was negative for cryoglobulin. Many examinations of the urine failed to reveal the presence of Bence-Jones protein. A blood culture was negative. The Congo red test for amyloid disease also proved negative. The patient excreted 57.5 per cent of a 100 microcurie dose of I^{131} in 48 hours. A precipitin test for trichinosis varied from a doubtful positive to 1–1280, but not in order of increasing titer. Roentgenograms of the chest and gall-bladder were noncontributory. Roentgenograms of the joints showed findings compatible with rheumatoid arthritis. Biopsy of gastrocnemius muscle and of deltoid muscle showed some areas of encysted trichinae. Other areas without trichinae revealed findings consistent with dermatomyositis. Several bone marrow examinations were not revealing.

Clinical Course: Neither Lugol's solution nor propylthiouracil affected the metabolism. The course was progressively downward with increasing weakness. Therapy with testosterone, intravenous procaine and para-aminobenzoic acid was without avail, and the patient was transferred to another institution for chronic care.

IV. Disorders of the Circulation

It is well known that patients with congestive heart failure have elevated basal metabolic rates.[38, 39, 40] Since various types of cardiac abnormalities (including auricular fibrillation) may exist with a normal metabolic rate until congestive failure appears, it would seem reasonable to attribute this to the fact that metabolic rates as measured on patients in congestive heart failure are not basal rates. Certainly a dyspneic, orthopneic and anxious patient is capable of demonstrating a metabolic rate of the order of + 25 per cent without invoking a more profound cause for the increased oxygen consumption. However, patients with minor degrees of anxiety and functional heart disease have normal metabolic rates.[41]

The problem of hypermetabolism in cases of essential hypertension is somewhat more complex. Boothby and Sandiford [2] demonstrated an increase in the basal metabolic rate in 50 per cent of 170 patients with essential hypertension. Crile and McCullagh [42] described a number of patients with hypermetabolism who closely mimicked the syndrome of thyrotoxicosis but who, on later examination, were classified as cases of essential hypertension. These patients had metabolic rates ranging from + 15 to + 77 per cent, with an average of + 33 per cent, and were said not to be in congestive heart failure.

Mountain, Allen and Haines [43] found a positive correlation between metabolic rates and average systolic pressure, although most of the cases observed in this series did not have very high metabolic rates. Using the much more accurate Tissot method for measuring basal metabolism, this

problem was investigated by Rosenkrantz and Marshall.[44] In a series of 115 patients with essential hypertension who were not in congestive failure, they found that 26.1 per cent had metabolic rates over + 10 per cent, 17.4 per cent had rates over + 15 per cent and 12.2 per cent had metabolic rates under — 10 per cent. These workers also found a direct correlation between metabolic rate and the level of blood pressure. Since hypertension is one of the features of hyperthyroidism, it is necessary to examine the evidence in order to exclude the possibility of atypical toxic diffuse goiter. Kahler and Winkler [45] observed that the hypermetabolism in these patients did not respond to iodine therapy. Bürger and Möbius [46] estimated the total blood iodine in patients with essential hypertension and found no correlation between blood iodine and basal metabolic rate. Silver and his co-workers [47] investigated a series of patients with extrathyroidal hypermetabolism and showed that among the essential hypertension group those exhibiting increased metabolic rates had normal plasma protein-bound iodine and a normal urinary excretion of radioiodine. These findings are inconsistent with a thyroidal mechanism. The observation made by Becker [48] that increased metabolic rates in hypertension may be corrected by roentgen irradiation to the thyroid gland does not prove necessarily an abnormal thyroid component, since removing the thyroidal contribution to the basal metabolic rate would lower a rate elevated through a nonthyroidal mechanism.

It is the conviction of the present authors that hypertension, per se, does not produce an elevated basal metabolic rate. When hypertension and hypermetabolism coexist, the latter may be due to (a) anxiety state, (b) congestive failure, (c) masked hyperthyroidism, and/or (d) pheochromocytoma.

Aortic stenosis apparently can result in extrathyroidal hypermetabolism of severe degree [49]; at present, no explanation is available to account for this phenomenon. The increased cardiac output in patients with arteriovenous aneurysm may cause an increase in oxygen requirements sufficient to elevate the basal metabolic rate.[47]

V. Neoplastic Disorders

Silver and his co-workers [47] noted that in various neoplastic disorders, including carcinoma (localized and metastatic), multiple myeloma and lymphomas (Hodgkin's disease, lymphosarcoma, lymphoblastoma, reticulum cell sarcoma, etc.), the basal metabolic rate was significantly elevated. In 23 patients with carcinoma, the basal metabolic rate was increased from 6 to 57 per cent above normal; in 11 patients with multiple myeloma from 14 to 60 per cent above normal, and in 14 patients with lymphomas from 11 to 65 per cent above normal. They ascribed the increased metabolism in these disorders to two factors: (a) the metabolic requirement of a large mass of active cells, and (b) the accumulation of calorigenic agents such as amino acids and polypeptides in degenerating tumors.

VI. Disorders of the Skin

Since hypermetabolism can be caused by either increased heat production or decreased heat loss (fever), it is reasonable to postulate that the diffuse erythrodermas may exhibit hypermetabolism because of the increased cellular metabolism of the skin.

The following case is illustrative of hypermetabolism secondary to diffuse erythroderma.

Case 2. A 65 year old male shirtmaker was admitted to the hospital on November 11 and died eight months later.

History of Present Illness: About two months prior to admission, the patient was engaged in house painting. He used kerosene and other (unknown) solvents to remove the paint from his hands. Two days later his hands became red and began to itch. The redness soon spread to his forearms and legs. The itching of the involved areas became severe. About five weeks before admission the eruption had become generalized.

Past, Personal and Family Histories: These were noncontributory.

Physical Examination: Hearing was considerably impaired; the eyes revealed no stare or lid lag; the mouth was edentulous; the tongue was moderately smooth, geographic and magenta-colored; the thyroid gland was not palpable; the breathing was emphysematous, with occasional coarse rhonchi heard at the right base; the heart was not enlarged; the blood pressure was 138 mm. Hg systolic and 64 mm. diastolic; the liver and spleen were not palpable; sacral and peripheral edema were graded +; no tremor of the fingers was noted. Examination of the skin revealed the following: The scalp showed fine brawny scaling; there was a generalized erythema with varying degrees of exfoliation, the scales averaging about 1 cm. in diameter; scaling was most marked over the extensor surfaces of the extremities and the back; the abdomen, chest and flexor aspects of the extremities showed only moderate scaling. The nails were thickened, with heaping up of epidermis beneath them; the proximal halves were roughened and irregular, the distal halves smooth. The palms and soles were considerably thickened and showed moderate fissuring.

Laboratory Examinations: The basal metabolic rate on two separate occasions was 28 and 42 per cent above the average normal, respectively; the blood count showed a mild secondary anemia and a leukocytosis of 13,000, with 10 per cent eosinophils; urinalysis was normal, with a specific gravity of 1.020; blood chemistry revealed the absence of nitrogen retention, a mild hypocholesteremia of 140 mg. per cent, a normal plasma chloride, and slightly decreased total serum proteins due to depression of the albumin fraction; the galactose tolerance test was equivocal, the one-hour reading in whole blood being 48.2 mg. per cent; a urine assay for thiamin, riboflavin and niacin gave normal values; the sedimentation rate was 68 mm./hour. A biopsy of a left axillary node revealed dermatopathic lymphadenitis; a biopsy of the skin from the abdominal wall was first interpreted as showing evidence of lymphoblastoma but, on later examination, features of mycosis fungoides were revealed. Roentgenograms of the chest showed considerable enlargement of the tracheal and mediastinal nodes, with calcification, moderate old hilus and bronchial thickening and pleural thickening on the lower right side. A barium colon enema and gastrointestinal series were reported as negative. An electrocardiogram proved to be normal.

Clinical Course: During the eight months of hospitalization, the intensity of the skin lesion varied considerably, and for the most part treatment consisted of superficial roentgen-ray therapy. The clinical course was complicated by bronchopneumonia, acute urinary retention due to a benign hypertrophy of the prostate gland,

acute cardiac decompensation and, finally, myocardial infarction due to coronary thrombosis, from which the patient died. Permission for autopsy was not obtained. The case was signed out as mycosis fungoides and dermatitis exfoliativa, generalized; bronchopneumonia of undetermined origin; benign hypertrophy of the prostate; arteriosclerotic heart disease; myocardial infarction due to arteriosclerotic coronary thrombosis.

Comment: Hyperthyroidism was excluded in this patient on the basis of the following findings: There were no eye signs, tremors, goiter or heat intolerance; moreover, the galactose tolerance test was not abnormal. It should be noted that the basal metabolic studies were done during the early part of his hospital stay, i.e., before the development of the complications that finally resulted in death.

VII. Disorders of the Nervous System

Hypothalamic, cortical or motor disturbances may be responsible for extrathyroidal hypermetabolism.

The hypothalamic center is known to be responsible for the maintenance of body temperature and may well affect heat production. A postencephalitic syndrome with hypermetabolism has been described,[50] but unfortunately, at the time this work was done, the technic of evaluation of thyroidal function had not been developed. The possibility that some of these patients had atypical toxic diffuse goiter cannot be excluded. Ten cases of presumptive hypophyseal or midbrain disease with diabetes and hypermetabolism have been described by Man and Peters.[5] The hypermetabolism did not respond to Lugolization, and those patients who were thyroidectomized failed to show a decrease in the basal metabolic rate.

The rôle of cortical dysfunction is harder to evaluate. It is generally recognized that individuals with the anxiety syndrome may exhibit hypermetabolism. It is likely that most of these cases fall into the category of disturbances of the motor system, since their muscular tension is sufficient to explain the elevated metabolic rate. Properly sedated, these patients exhibit normal oxygen consumption, in contradistinction to the hypermetabolism of hyperthyroidism, which is not influenced by sedation.[51]

Patients with frank psychoses appear to exhibit normal metabolic rates if careful technic is used. These patients are notoriously poor subjects for metabolic measurement.[52, 53]

It appears unnecessary to discuss disturbances of motor function in detail. Obviously, patients exhibiting tremor, tic, spasticity, muscular spasm and voluntary muscular tension are not in the basal state and their measured metabolic rates are meaningless. Apparently, some individuals can voluntarily increase their oxygen consumption. One patient studied by Carpenter, Hoskins and Hitchcock [54] was able to raise his metabolic rate from — 9 to + 25 per cent under what appeared to be basal conditions. The increase was accompanied by an augmentation in pulse rate, but the tachy-

cardia could hardly account for such a decided increase in metabolism. Most likely, muscular tension was the factor involved. Willard and Wolf [55] have shown that a trained subject can alter his metabolic rate voluntarily ± 100 per cent by varying his chest volume in such a manner as to be undetectable to a trained technician.

VII. Disorders of the Osseous System

As in arteriovenous aneurysm, the increased cardiac output in patients with Paget's disease of bone may cause an increase in oxygen requirement sufficient to elevate the basal metabolic rate significantly.[47]

IX. Hemochromatosis

Duncan [56] states that moderate elevations in the basal metabolic rate are not uncommon in this disorder. It is difficult to explain this phenomenon.

X. Drugs

The mechanism by which certain chemical agents produce hypermetabolism is unknown, but the fact that such substances exist is of clinical importance.

A and B. *Thyroid and Thyroxine:* The specific stimulating effect of thyroid substance and of thyroxine on oxygen consumption has been appreciated for a long time. In fact, the hypermetabolism of thyrotoxicosis is due to increased circulating thyroxine. Extrathyroidal hypermetabolism may at times be due to excessive intake of these metabolic stimulants. The covert ingestion of thyroid substance (thyrotoxicosis factitia [57]) should be suspected in cases which exhibit the clinical findings of hyperthyroidism yet which have a normal or increased excretion of a tracer dose of radioactive iodine.

C. *Epinephrine:* This metabolic stimulant has been discussed previously under Disorders of the Endocrine System.

D. *Ephedrine:* Since this drug is widely used in the treatment of bronchial asthma, it is of interest to note that it causes hypermetabolism. Starr and his co-workers [16] showed that 50 to 67.5 mg. administered subcutaneously (six patients) caused an average increase of 14.2 per cent in the basal metabolic rate.

E. *Caffeine:* The xanthines, especially caffeine, tend to increase the basal metabolic rate. Means, Aub and DuBois [58] found that doses of 0.5 to 0.65 gm. of caffeine increased the basal rate in man 7 to 23 per cent; the maximal rise occurred in one to three hours, without a concomitant increase in pulse rate or body temperature. Apparently, smaller doses do not influence oxygen consumption, as shown by Boothby and Rowntree [59] and by Grollman.[60] Starr and his associates [16] found that the intramuscular injection of 0.5 gm. of caffeine sodium benzoate in four subjects increased heat pro-

duction in one, slightly increased it in two and decreased it in one; the average increase was 6.9 per cent. Womack and Cole [61] showed that large doses of caffeine increased the basal metabolism of guinea pigs 40 to 75 per cent.

The following clinical report probably represents a case of extrathyroidal hypermetabolism due to the ingestion of excessive amounts of caffeine. It is impossible to state whether the increased heat production in this patient was due to an anxiety state resulting from abnormal coffee drinking or to a direct effect of caffeine on oxygen consumption at a cellular level. In view of the fact that tachycardia was not present, it is probable that the hypermetabolism was due to the specific effect of caffeine on oxygen consumption.

Case 3. A 40 year old housewife was admitted to the Combined Medical and Surgical Thyroid Clinic. The chief complaints were progressive swelling of the neck, weight gain of 60 pounds and nervousness for the past 12 months.

Physical Examination: The patient appeared placid; there was generalized obesity; no exophthalmos was present; the right lobe of the thyroid gland was diffusely enlarged without thrill or bruit; the fingers revealed a slight tremor.

TABLE II

Decrease in Basal Metabolism in a Patient with Possible Caffeine Poisoning (Excessive Coffee Intake) Following the Elimination of Coffee From the Diet

Date (weeks)	B. M. R.* (% of average normal)	Pulse Rate (no. per min.)	Weight (pounds)
0	+36	84	178
4	+24	76	178
14	+15	64	167
33	+12	62	170
42	+ 8	72	174
63	+ 2	60	180

* These determinations were done by the open Tissot method in the Respiration Laboratory of Dr. Cameron V. Bailey and are considered highly accurate.

Laboratory Examinations: The basal metabolic rate was + 36 per cent, with a pulse rate of 84 per minute. Although the diagnosis of "plump" hyperthyroidism was entertained at first, the weight gain of 60 pounds in one year was unusual. For this reason, a detailed dietary history was taken. The patient stated that she drank 45 to 50 cups of coffee daily and consumed excessive amounts of carbohydrates. At this point, a diagnosis of caffeine intoxication was considered. The patient was advised to abstain from coffee completely, and a low caloric diet was prescribed. Table 2 reveals the decline in the basal metabolic rate, which is ascribed to the elimination of coffee from the diet. Inasmuch as the patient was unable to reduce her intake of calories, the decrease in basal metabolism was not due to inanition. This table reveals a very slow recession of the basal metabolic rate following the cessation of coffee drinking. The reason for this phenomenon may be that the excessive intake of caffeine for months or years established what Bailey [62] calls a "new metabolic habit." Under such a circumstance, eliminating the stimulant would produce a slow decline in oxygen consumption of cells previously primed to high oxygen intake.

F. *Histamine:* The intravenous administration of histamine may cause an elevation of the metabolic rate by 50 per cent.[63]

G. *Dinitrophenol:* The mechanism of the calorigenic action of this drug is completely unknown.[64, 65] However, the fact that dinitrophenol produces in vitro stimulation of oxygen consumption implies an extrathyroidal mechanism. Clinical evidence also substantiates this view, since none of the features of thyrotoxicosis is produced by this substance and the blood cholesterol remains at normal levels.[66]

H. *Theophylline-ethylenediamine (Aminophylline)*: Starr and his coworkers [16] showed that the intramuscular injection of 0.48 gm. of this drug into seven subjects increased the metabolism in five, decreased the metabolism in one and produced no change in one; the average increase in the metabolic rate was 7.8 per cent.

XI. Pregnancy

The hypermetabolism of pregnancy is well recognized. Since the increase is notable only in the last trimester, the simplest view of this phenomenon would be that the mother with a distended abdomen is not in a basal state. However, evidence has been offered to show that the observed rate is equal to the sum of maternal and fetal rates computed on the basis of body surface.[67] That this explanation does not account for a portion of the increase is shown by the work of Rowe and Boyd.[68] In any case, this type of hypermetabolism is rarely of clinical interest.

XII. Fever

It is clear that any factor producing fever will increase oxygen consumption of cells and thus raise the metabolic rate. DuBois [69] plotted the increase in the rate of metabolism against the body temperature in six types of fever and found the average coefficient to be 2.3. This value agrees (accepting an error of $\pm$ 10 per cent) with van't Hoff's law, which states that the velocity of ordinary chemical reactions increases between two and three times with a rise of 10° C.

XIII. Technical Errors

The magnitude of possible errors in the measurement of the basal metabolic rate is not generally appreciated. Technical errors may produce in normal subjects basal rates as high as + 70 per cent and the same false hypermetabolic rates obtained repeatedly in the same individual. These errors may be with the technician, the apparatus or the patient.

The technician must possess several indispensable attributes: (a) basic knowledge of what is being determined; (b) complete familiarity with the apparatus, and (c) facility for placing the patient at complete ease. The last requires a short, lucid explanation to the patient of the mechanics involved and the degree of coöperation desired. This must be done in a quiet, self-assured manner in order to inspire complete confidence and promote maximal body relaxation.

The choice of the apparatus is, of course, important. The commonly used Sandiford closed system device requires very careful attention to detail if accurate results are to be obtained. For institutional work, the open method of Tissot is strongly recommended.[70] Regardless of type, the apparatus must be checked frequently for leaks, especially at the rubber connections.

As for the patient, the greatest care must be exercised in order to insure the basal state. This involves more than the fasting state after an adequate night's sleep. Complete relaxation of the patient, mind as well as muscles, is a sine qua non. For this reason, the basal state is difficult if not impossible for some individuals to attain. Nervous and anxious patients are best prepared by the use of sedatives and soporifics for 24 hours before the procedure is carried out or, as Bartels [51] has suggested, by the use of pentothal anesthesia. During the test, the subject should be watched carefully for undue air swallowing (aerophagia), which may be done at so regular a rate as to fail detection by examination of the tracing. Salivation induced by the rubber mouthpiece may cause discomfort and consequent muscle tension. A perforated ear drum with a patent Eustachian tube will, of course, lead to erroneous results.[71, 72] Since voluntary variations in chest capacity may significantly alter the basal metabolic rate,[55] inadvertent changes in chest excursions should be noted. Forced hyperventilation for four minutes may increase the basal rate as much as 43 per cent.[73] Of course, marked hyperventilation of this duration could not escape detection, but significant elevations in the basal rate might result from less obvious forced breathing. Finally, it should be noted that a patient in pain is not in a basal state, irrespective of the preparation. Pain in a knee joint, for example, should be alleviated by placing a small pillow under the knee, thus reducing the muscle tension and spasm. In these patients, the judicious use of analgesics for several hours prior to the test is often indicated.

Summary

The clinical, physiologic and physical factors producing extrathyroidal hypermetabolism are classified and discussed. Three cases illustrating hypermetabolism due to dermatomyositis, diffuse erythroderma and caffeine poisoning, respectively, are reported.

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DISTURBANCES OF CARDIAC RHYTHM AND CONDUCTION IN CONGENITAL CARDIAC DISEASE: REPORT OF 5 CASES *

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Interest in congenital cardiac disease has stimulated many reports dealing with the anatomic, physiologic and clinical aspects of anomalies of the heart. Disturbances in cardiac rhythm and conduction in association with congenital cardiac disease comprise an important but less commonly recorded finding in congenital cardiac disease. Complete heart block is probably the most commonly recorded conduction disturbance observed in association with congenital cardiac disease. This ectopic rhythm is most often observed in association with congenital ventricular septal defects. Auricular fibrillation has been observed by Taussig [1] to occur frequently in association with defects of the atrial septum. This anomaly may also be associated with paroxysmal tachycardia, auricular flutter and complete heart block. Dry [2] has recently recorded a case of paroxysmal tachycardia with an atrial septal defect, in which death was presumably the result of the ectopic rhythm. Bodlander [3] has observed the Wolff-Parkinson-White syndrome in association with coarctation of the aorta. Auricular flutter and congenital heart disease were observed by Prince, Rotondo and Scott.[4] The type of congenital anomaly in the case reported by these authors could not be proved, but the anomaly was assumed to be congenital because the arrhythmia was observed shortly after birth.

Recorded arrhythmias and disturbances in cardiac conduction in association with congenital cardiac disease, however, are not common. Uhley,[5] in an electrocardiographic analysis of 53 cases of congenital cardiac disease observed clinically and at necropsy at the Michael Reese Hospital in Chicago, observed disturbances of atrioventricular conduction in only three cases. In two of these cases atrioventricular heart block, grade 1, was present. The pathologic anatomic diagnosis in these cases was aortic atresia in one and congenital bicuspid aortic valve in the other. In the third case of ectopic rhythm in Uhley's series, auricular fibrillation occurred in a patient of 70 years with a patent foramen ovale measuring 1 cm. No arrhythmia was recorded in this series.

Other cardiac arrhythmias may develop in utero or appear at an early age in life without other demonstrable evidence of congenital cardiac disease. In these cases, Taussig has emphasized that it is often impossible even at necropsy to prove that these arrhythmias were due to congenital anomalies of the atrial musculature. Regardless of whether these arrhythmias are

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considered true congenital anomalies, Taussig [1] considers them to be abnormal.

It is the purpose of this report to record two cases with arrhythmias and one case with an acquired cardiac conduction disturbance observed in association with congenital cardiac disease. Also, two arrhythmias of probable congenital origin, one developing in uterine life and one in infancy, are reported.

Case Reports

Case 1. Eisenmenger's Complex Associated With Supraventricular Tachycardia. Clinical Features: The patient was a white man, aged 22 years at the time of his first examination in December, 1948. A cardiac murmur had been observed shortly after birth. Minimal cyanosis had been present since birth. Dyspnea had never been severe. There was no past medical history of childhood infections. The physical and mental development of the patient had been normal.

The pulse rate was 72 beats per minute. The blood pressure was 120 mm. of mercury systolic and 80 diastolic. Minimal cyanosis of the mucous membranes was observed. Palpation of the chest revealed a systolic thrill maximal in intensity over the third left interspace, with transmission to the fourth and fifth left interspaces. There was a systolic murmur, grade 4, of maximal intensity over the third left interspace, with transmission over the rest of the precordium. Minimal clubbing of the digits was observed.

There were 4,760,000 erythrocytes and 7,400 leukocytes per cubic millimeter of blood, and 14.5 gm. of hemoglobin per 100 c.c. of whole blood. The electrocardiographic examination revealed right axis deviation (figure 1*a*). The auricular and ventricular rates were 80 beats per minute. The PR interval measured 0.16 second, and the QRS time was 0.08 second. Prominent S waves were present in Leads I and II. Roentgenographic examination of the thorax revealed the presence of cardiac enlargement (figure 1*b*). The pulmonary artery was enlarged and with roentgenoscopic examination was observed to pulsate actively. No abnormal pulsation of the hilar vessels was present. The barium-filled esophagus showed normal deviation for the aorta, but no abnormal displacement at the level of the atria. The right border of the heart was unusually prominent. The cardiac measurements were M. R., 6.0 cm.; M. L., 8.1 cm.; transverse thoracic diameter, 26.2 cm. The cardiac-thoracic ratio was 54 per cent.

The patient was next observed on February 22, 1950. At this time, sudden palpitation of the heart associated with dyspnea and profuse perspiration had developed. There was an associated sense of constriction of the thorax, accompanied by apprehension.

The physical examination revealed an acutely ill white man. There had been a marked increase in cyanosis. The pulse was of poor quality. The rate was approximately 200 beats per minute. The blood pressure was 90 mm. of mercury systolic and 70 diastolic. Profuse perspiration covering the head and thorax was present. The apex rate was 240 beats per minute. Râles were present in both bases.

Three grains (about 0.2 gm.) of quinidine sulfate was administered. Carotid pressure was ineffectual in controlling the ectopic rhythm. In view of the cardiac failure which was present, the patient was hospitalized. Oxygen was administered by means of a tent. Ten milligrams of methacholine chloride (mecholyl chloride) were administered subcutaneously without benefit. Three grains (about 0.2 gm.) of quinidine sulfate was administered every fourth hour. An electrocardiogram (figure 2) revealed supraventricular tachycardia. The ventricular rate was 210 beats per minute. P waves could not be identified. The QRS complexes measured

0.08 second. The T waves were upright in Leads I and II and in CF leads. Right axis deviation was present. The paroxysmal supraventricular tachycardia persisted for 36 hours, decreasing from 240 to 200 beats per minute. On the morning of February 24, the paroxysm stopped and the heart rate returned to normal. Improvement of cyanosis was observed promptly.

The patient has been observed at frequent intervals since this time. Administration of quinidine in a maintenance dosage has been continued. There had been no return of ectopic rhythm at the time of his latest examination, in July, 1950.

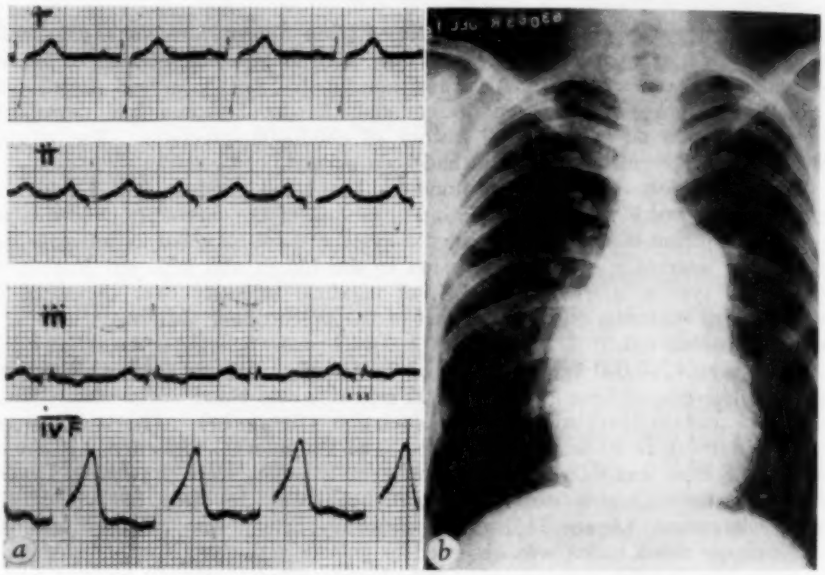

FIG. 1 (*Case 1*). Eisenmenger's complex. *a*. Sinus rhythm. *b*. Prominent pulmonary artery.

Comment on Case 1: The diagnosis of congenital cardiac disease is well established in this case. The clinical features of cyanosis observed first at birth, associated with a loud systolic murmur and thrill of greatest intensity at the third left interspace, minimal clubbing of digits, right axis deviation in the electrocardiogram and a prominent pulmonary arterial segment revealed by roentgenographic examination of the thorax, established the probable clinical diagnosis of Eisenmenger's complex.

The development of paroxysmal supraventricular tachycardia created a grave complication in this case of congenital cardiac disease in view of the severe degree of congestive cardiac failure created by the arrhythmia. Methacholine chloride was ineffective in stopping the tachycardia, but quinidine sulfate eventually controlled the ectopic rhythm in the case under discussion. With cessation of the acquired arrhythmia, evidence of congestive cardiac failure disappeared.

*Case 2. Congenital Ventricular Septal Defect With Acquired Complete Heart Block.** Clinical Features: The patient was a white boy of two and one-half years. At the time of first examination, on March 20, 1947, no cyanosis had been observed. The physical examination revealed the pulse rate to be 100 beats per minute. The blood pressure was 100 mm. of mercury systolic and 80 diastolic. There was a systolic murmur, grade 3, of maximal intensity at the third left interspace, associated with a systolic thrill at the same area.

An electrocardiogram revealed normal sinus rhythm (figure 3*a*). The auricular and ventricular rates were 120 beats per minute. The PR interval measured 0.16 second and the QRS complex 0.08 second. A roentgenogram of the thorax revealed marked prominence of the left side of the heart. There was a characteristic wooden-shoe appearance to the cardiac silhouette. The clinical diagnosis of congenital ventricular septal defect was made.

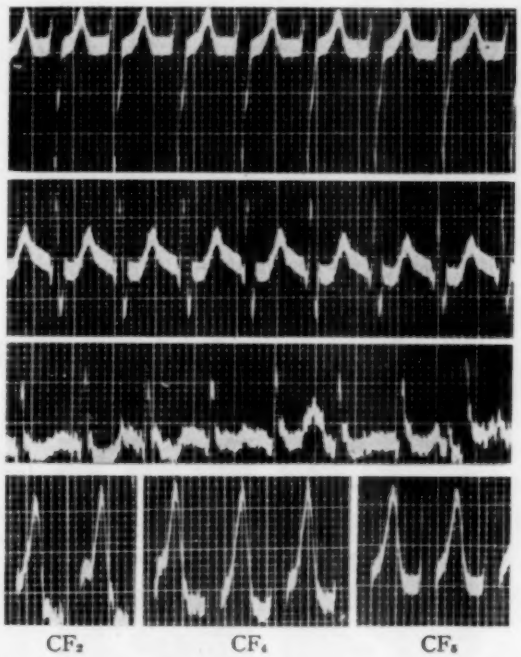

FIG. 2 (*Case 1*). Eisenmenger's complex, supraventricular tachycardia.

The child's subsequent course was uncomplicated for one and a half years. On January 8, 1949, an attack of Adams-Stokes syncope occurred. The pulse rate at this time was 48 beats per minute. The electrocardiogram now revealed complete heart block (figure 3*b*).

During the subsequent six months, persistent complete heart block was observed with recurrent attacks of Adams-Stokes syncope. Death occurred suddenly in August, 1949, during an attack of Adams-Stokes syncope.

Pathologic Features: At necropsy, the pertinent findings were confined to the heart and great vessels. There was a large defect involving the membranous portion of the ventricular septum. The aorta arose exclusively from the left ventricle.

*This case has been reported in detail elsewhere.[6]

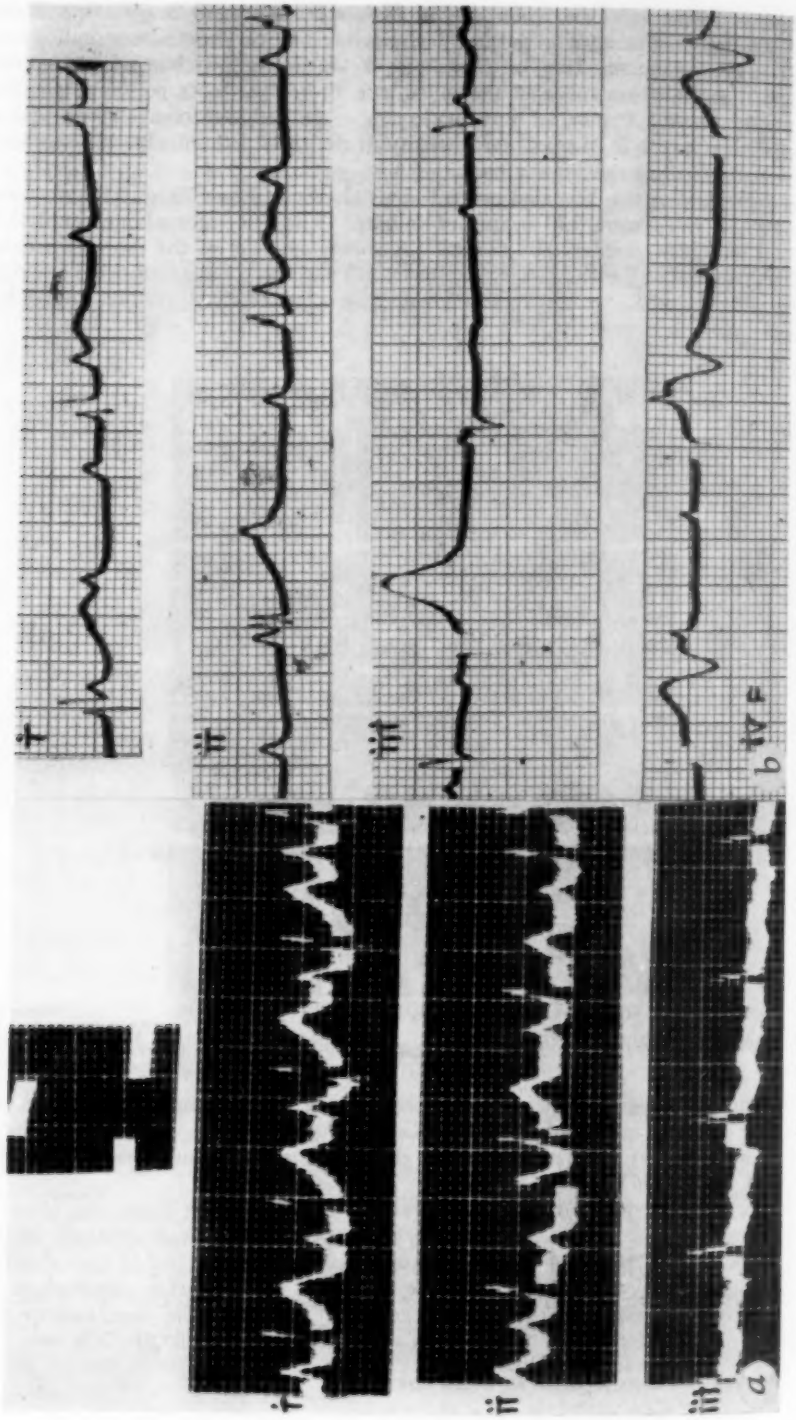

FIG. 3 (*Case 2*). Ventricular septal defect. *a*. Sinus rhythm. *b*. Complete heart block.

The pulmonary trunk was narrower than normal. There was an associated malformation of the aortic arch, consisting of a right aortic arch with a vascular ring around the trachea and the esophagus.

Comment on Case 2: This case is an example of acquired complete heart block with Adams-Stokes attacks occurring in the presence of congenital ventricular septal defect. The number of cases of congenital heart block studied at necropsy is small. In 1938 Wallgren and Winblad [7] collected 11 cases of congenital heart block studied at necropsy, including two reported by them. Congenital heart block is most often associated with a ventricular septal defect. It has been observed with cor triloculare biatriatum, complete transposition of the great vessels, patent ductus arteriosus, absent atrial septum and tricuspid atresia.

The association of congenital cardiac disease with acquired complete heart block is much less common than its association with congenital complete heart block. The only cases comparable to the one here recorded are those reported by Laubry and Pezzi [8] and by Yater, Barrier and McNabb.[9] In the case of Yater and associates there was a persistent ostium primum.

The presence of Adams-Stokes attacks in association with congenital complete heart block is rare. In 1939 Faessler [10] collected from the literature eight cases in which Adams-Stokes attacks associated with congenital heart disease occurred in children less than two years of age. To this series she added one case of her own with Adams-Stokes attacks due to atrioventricular nodal rhythm. In six cases of this series there was complete heart block between attacks. The pathologic diagnosis in Faessler's series of nine cases was ventricular septal defect in six instances; patent ductus arteriosus in one; patent foramen ovale in one, and transposition of the great vessels associated with pulmonary stenosis and ventricular septal defect in one. Crawford and DiGregorio [11] stated that Adams-Stokes attacks were not common in the younger age group, and while sudden death in young persons with complete heart block is rare, this possibility existed.

*Case 3. Supraventricular Tachycardia Associated With Coarctation of the Aorta (Infantile Type).** Clinical Features: The patient was a male infant born on June 5, 1950. The child had a normal birth, at full term. The birth weight was 6 pounds and 12 ounces (about 3.0 kg.). No cyanosis was observed. The results of physical examination were normal. After seven days of hospitalization the infant was dismissed.

Two days after dismissal from the hospital, exhaustion and dyspnea after feeding were observed by the infant's mother. On June 15, pallor and marked dyspnea occurred. The physical examination at this time revealed the apex rate to be approximately 200 beats per minute. The respiratory rate was 75 per minute. Hospitalization was advised.

On admission to the hospital the temperature was 98.6° F. and the apex rate was more than 200 beats per minute. The respiratory rate was approximately 100 per minute. Although respiration was rapid and labored, the lungs on physical examination were clear to auscultation and percussion. Auscultation of the heart

*The patient was attended by Dr. John H. Cordes, Jr.

revealed a gallop rhythm. No murmur was heard. The liver was enlarged, extending to the umbilicus. The spleen was palpable 2 cm. below the left costal margin.

The respirations soon became more labored. Minimal cyanosis developed. Oxygen was administered by means of a tent. One grain (about 0.065 gm.) of quinidine sulfate was administered orally. This was increased 0.5 gr. (about 0.032 gm.) every second hour, until the maximal dosage of 2.5 gr. (about 0.16 gm.) every second hour was obtained. On June 16 the patient appeared improved. The apex rate was 150 beats per minute. The respiratory rate was 150 per minute. Administration of quinidine was discontinued because it appeared to make the infant more restless and irritable.

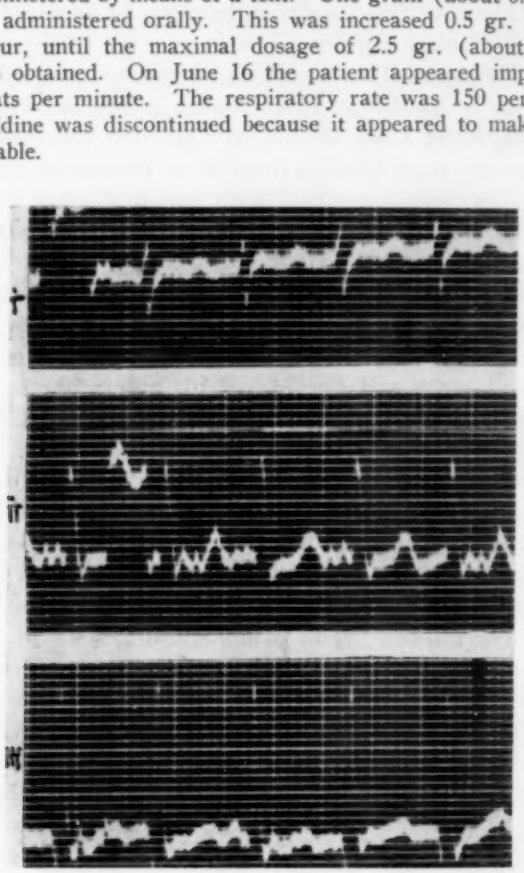

FIG. 4 (*Case 3*). Infantile coarctation of the aorta, supraventricular tachycardia.

The electrocardiogram (figure 4) revealed the ventricular rate to be 150 beats per minute. No P waves could be identified. Minimal right axis deviation was present. The QRS complex measured 0.08 second. The T wave in Lead I was diphasic. The electrocardiographic diagnosis was supraventricular tachycardia. In the absence of identifiable P waves, inspection of the QT intervals failed to reveal evidence of variation that would assist in identifying a P wave superimposed on the preceding T wave. It therefore seems more probable that this ectopic rhythm was a supraventricular tachycardia rather than partial heart block with tachycardia.

Laboratory examinations showed that: erythrocytes numbered 3,310,000 and leukocytes 15,000 per cu. mm. of blood, and the hemoglobin was 11 gm. per 100 c.c. of whole blood.

On June 16, three-eighths grain (about 0.024 gm.) of digitalis (whole leaf) was administered orally. Subsequently respirations became more labored and

cyanosis developed. Edema of the extremities was observed. Death occurred on the evening of June 16, at the age of 11 days. The clinical diagnosis was supraventricular tachycardia with congestive heart failure. Congenital cardiac disease was suspected but not classified.

Pathologic Features: At necropsy, the pertinent findings were confined to the heart, which weighed 23 gm. The foramen ovale was anatomically patent but physiologically closed. The ventricular septum was intact. The aorta and pulmonary trunk bore a normal relationship to each other. The aortic arch gave origin to the innominate and left carotid and subclavian arteries. The aorta revealed tubular constriction for a distance of 3.0 mm., originating distal to the left subclavian artery and proximal to the ductus arteriosus. At this point the lumen of the aorta measured 1.0 mm. in diameter, while on either side of the constriction it measured 3.0 mm. in diameter. The ductus arteriosus, which arose from the left pulmonary artery, was widely patent and measured 3.0 mm. in diameter.

Comment on Case 3: In this case, supraventricular tachycardia associated with infantile coarctation of the aorta resulted in death in infancy. Calodney and Carson [12] analyzed data on 21 cases of coarctation of the aorta, observed clinically and at necropsy. These authors emphasized the clinical findings that will lead to an early diagnosis. Ectopic rhythms were not recorded as occurring spontaneously in this series, with the exception of one case in which operation was performed and in which death was presumed to be the result of ventricular fibrillation.

In the present case the ectopic rhythm, while associated with congenital cardiac disease, was acquired on the tenth day of life. The onset of the arrhythmia was dramatic and contributed to the death of the patient in early infancy.

Case 4. Nodal Tachycardia of Probable Congenital Origin. Clinical Features: The patient was a white boy of nine years at the time of first examination on March 19, 1948. The chief symptom at this time was substernal thoracic pain. Tachycardia, which was first observed in prenatal life, had been present since birth. The attending obstetrician had observed prior to delivery that the fetal heart rate was rapid, being more than 200 beats per minute. After birth, January 4, 1939, on the basis of numerous electrocardiograms, a diagnosis of nodal tachycardia was made. Quinidine was then administered to the infant, without benefit. This medication was followed by elixir phenobarbital, which produced some slowing of the heart rate, but the pulse was never as slow as would be anticipated in the case of a normal infant. Since birth, the heart rate had varied from 120 to 180 beats per minute. No cyanosis had been observed at birth, but slight cyanosis had been observed prior to the examination in 1948.

Physical examination revealed a well-developed white boy of nine years. The pulse rate was 120 beats per minute and irregular in rhythm. The blood pressure was 106 mm. of mercury systolic and 80 diastolic. No cardiac murmur or thrill could be demonstrated. No clubbing of the digits was observed.

The electrocardiogram (figure 5) revealed short paroxysms of rapid heart action lasting for five to seven seconds, during which time the heart rate was 160 beats per minute. The paroxysms of tachycardia were followed by short periods consisting of two or three beats that originated with a normal sinus rhythm. The PR interval preceding the normal beats was 0.16 second. During the period of tachycardia the PR interval varied from 0.08 to 0.10 second. The P wave was at times upright and

in other strips of the electrocardiogram the P waves were inverted. The QRS time was 0.08 second. The T waves were upright in Leads I and II, with inversion of the T wave in CF_4.

The roentgenographic examination of the thorax revealed clear lung fields. No cardiac enlargement was present. No abnormal indentation of the barium-filled esophagus was present. Irregularity of the cardiac pulsations was observed. The cardiac measurements were M. R., 3.4 cm.; M. L., 6.2 cm.; transverse thoracic diameter, 21.3 cm. The cardiac-thoracic ratio was 45 per cent.

Quinidine sulfate was administered in the dosage of 1 gr. (about 0.065 gm.) four times daily. The patient was next observed on April 8 and again on October 6, 1948. At this time there was no change in the results of physical examination, except for a rapid regular pulse at the rate of 150 beats per minute. The electrocardiogram (figure 6*a*) revealed nodal tachycardia. There was inversion of the P waves in Leads I and II. The PR interval varied from 0.10 to 0.12 second. The QRS time was 0.08 second. The T waves were upright in Leads I and II, but inverted in CF_4.

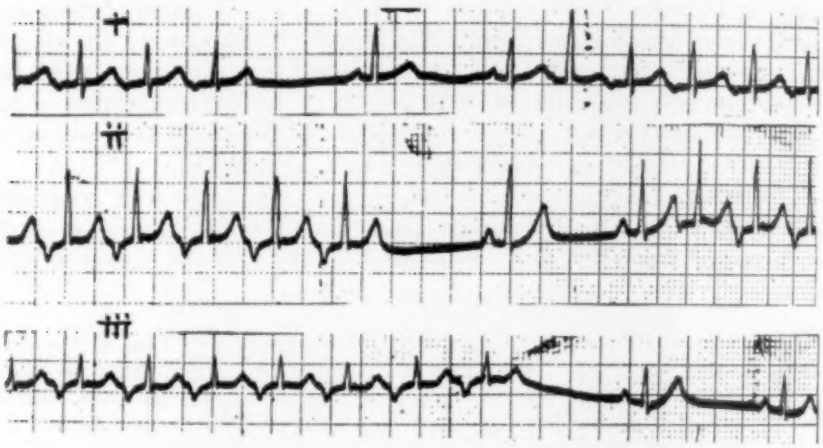

FIG. 5 (*Case 4*). Nodal tachycardia, occurring in paroxysms.

Comment on Case 4: The presence of rapid heart action observed in fetal life, with subsequent nodal rhythm at birth persisting through early childhood, establishes the congenital origin beyond any reasonable doubt in this case. Burchell [13] has suggested that some of the cases of reported congenital heart block may represent conduction disturbances acquired in utero. This hypothesis was strengthened in the case of congenital ventricular septal defect with acquired heart block. The possibility that in this case the nodal rhythm was acquired in utero can not be entirely eliminated.

The mechanism of the tachycardia in this case is of interest. Burchell [14] has suggested that this arrhythmia represents a reëntry phenomenon whereby the ventricular afterpotential is able to activate the auricle from below, perhaps through an accessory pathway such as a bundle of Kent. In this way it would represent a type of reciprocal rhythm. This type of reciprocal

rhythm utilizing the accessory pathway is much more acceptable as an explanation than thinking of a double pathway in the usual atrioventricular conduction pathway. The ineffectiveness of quinidine sulfate in controlling the tachycardia would best be explained by utilizing the hypothesis of an accessory pathway, since quinidine has so little effect on conduction.

Cases of tachycardia recognized prior to birth are not common but have been recorded by Carr and McClure,[15] Tollas [16] and Garvin and Kline.[17] The case of congenital paroxysmal tachycardia observed by Garvin and Kline

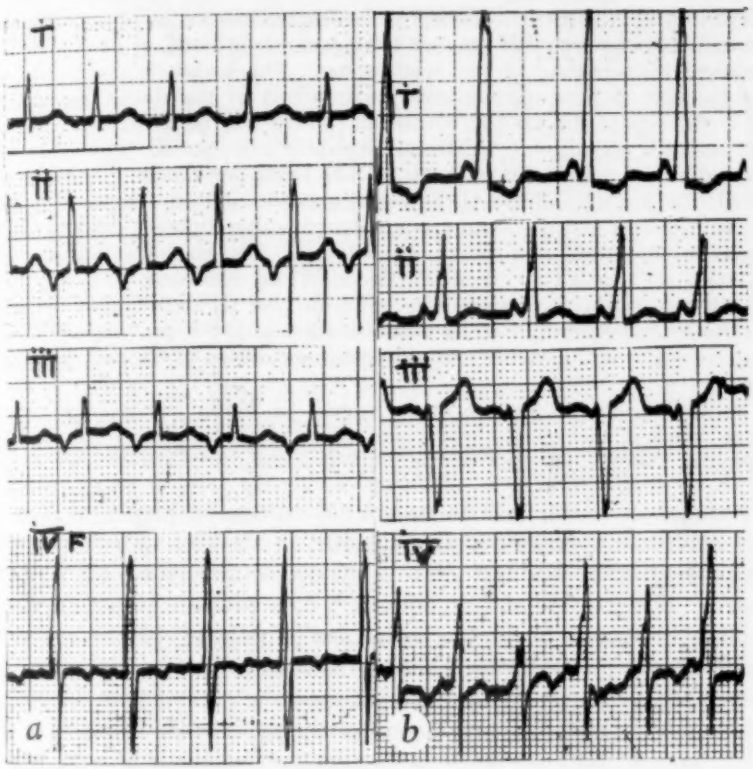

FIG. 6*a* (*Case 4*). Nodal tachycardia. *b* (*Case 5*). Wolff-Parkinson-White syndrome.

is very similar to that recorded herein. However, the patient observed by these authors, when examined at four months of age, appeared to have a normal cardiac rhythm. The fact that these cases of ectopic rhythm may be recognized during intrauterine life does not imply that there is underlying congenital malformation of the auricular musculature.

Case 5. Wolff-Parkinson-White Syndrome With Paroxysmal Tachycardia. Clinical Features: The patient was a colored girl of 18 months at the time of her first examination on January 11, 1950. The infant was born on June 16, 1948. At

the age of four months paroxysms of tachycardia appeared. The infant was examined by her pediatrician during the attacks of tachycardia, and apical rates of 200 to 220 beats per minute were observed. Cessation of attacks of paroxysmal tachycardia was accomplished by induced vomiting and the administration of quinidine sulfate. The attacks of rapid heart action would recur on the average of once monthly. Measles developed in December, 1949, and this infection was followed by a severe attack of paroxysmal tachycardia.

Physical examination revealed the pulse rate to be 120 beats per minute. The blood pressure was 100 mm. of mercury systolic and 60 diastolic. There was a systolic murmur, grade 2, heard at maximal intensity at the mitral area, but transmitted to the left costal margin.

Erythrocytes numbered 4,250,000 per cubic millimeter of blood. The concentration of hemoglobin was 7.75 gm. per 100 c.c. of whole blood, or 54 per cent. There was marked hypochromia of the erythrocytes. The leukocyte count was normal. Roentgenoscopic and roentgenographic examination of the thorax revealed no increase in the size of the cardiac silhouette. There was no abnormal indentation of the barium-filled esophagus. Electrocardiographic examination (figure 6*b*) revealed the auricular and ventricular rates to be 120 beats per minute. The PR interval measured 0.08 second and the QRS complex measured 0.10 second. The ST segment was depressed in Lead I and was associated with a diphasic T wave. The QRS complexes were slurred in Leads I, II and CF_4. The electrocardiogram was consistent with the pattern of Wolff-Parkinson-White syndrome. The electrocardiographic pattern in this case was consistent with type II, according to the classification of Burch and Kimball.[18] The administration of 1/500 gr. (about 0.00013 gm.) of atropine sulfate was ineffective in producing any change in the electrocardiographic pattern.

The patient was examined next on August 12, 1950. In the interim there had been one attack of tachycardia which was observed after recovery from chickenpox. The physical findings and electrocardiographic findings at this time were unchanged.

Comment on Case 5: The congenital nature of the Wolff-Parkinson-White syndrome appears to be established in view of those cases with the electrocardiographic findings of this syndrome that have been studied at necropsy. Butterworth and Poindexter [19] have produced electrocardiograms, in animals, with a short PR interval and prolonged QRS complex by an artificial accessory pathway. Wood, Wolferth and Geckeler [20] in 1943 demonstrated muscular connections between the right atrium and the right ventricle, which bridged a small part of the ventricular cavity during their course. Wood and associates stated that these structures were capable of conducting an impulse from atrium to ventricle. An anomalous band of muscle connecting the left atrium to the left ventricle, near the interventricular septum, was demonstrated by Öhnell.[21] Kimball and Burch [22] demonstrated two aberrant bundles of muscle tissue, one connecting the right atrium with the right ventricle and another connecting the left atrium with the left ventricle. This finding occurred in an infant of eight months, with paroxysmal tachycardia starting at the age of two weeks. The electrocardiogram after an attack of tachycardia revealed the Wolff-Parkinson-White syndrome.

The occurrence of this syndrome in early infancy is not common. In

1946 Littmann and Tarnower [23] could find no cases with this syndrome recorded as occurring in infancy. Bodlander [8] reported one case of the syndrome observed at the age of 14 weeks. In this case erosion of the ribs developed, as was demonstrated by roentgenographic examination at three years of age, and the clinical diagnosis of coarctation of the aorta was established. Prior to the reported case of Bodlander, four and one-half years was the earliest age at which the Wolff-Parkinson-White syndrome had been observed. This case was recorded by Hamburger.[24] This patient was again observed at the age of 24 years by Malinow and Langendorf.[25] The electrocardiographic findings had persisted but no symptom of cardiac disease had developed. In the case of Kimball and Burch,[22] attacks of paroxysmal tachycardia developed at two weeks of age, but the Wolff-Parkinson-White syndrome was not demonstrated electrocardiographically until the patient was 14 weeks of age. Schieve [26] demonstrated electrocardiographically the existence of the Wolff-Parkinson-White syndrome in an infant of five weeks. In the case reported herein, paroxysmal tachycardia was first observed clinically at four months of age, but the diagnosis of Wolff-Parkinson-White syndrome was not established by electrocardiographic examination until the patient was one and one-half years of age. The establishment of the diagnosis at this age places this case on record as another example of the syndrome of a short PR interval with a wide QRS time recognized at an early age. While examples of this syndrome occurring in infancy and childhood are not common, it is probable that if routine electrocardiograms were made in infants and children, particularly those with attacks of paroxysmal tachycardia, the syndrome would be diagnosed with greater frequency. Examples of the Wolff-Parkinson-White syndrome observed with other evidence of congenital cardiac disease are rare. The case of Bodlander, existing with coarctation of the aorta, has been mentioned.

Stein [27] observed the Wolff-Parkinson-White syndrome in a 27 year old with probable congenital cardiac disease. The clinical diagnosis of congenital cardiac disease was established by the physical findings of a cardiac murmur, clubbing of the digits, cyanosis, roentgenographic evidence of cardiac enlargement and laboratory evidence of a double end point in the ether circulation time. Wolff and White,[28] in reviewing 11 cases reported in their original communication and 41 new cases of the syndrome under discussion observed by these authors, found that none of the patients had other evidence of congenital heart disease or other congenital anomalies. Willius and Carryer,[29] in an analysis of 65 cases displaying short PR intervals wth prolonged QRS complexes, observed none existing with other evidence of congenital cardiac disease. These authors advised histologic study of a large series of normal human hearts to determine the evidence of accessory pathways of conduction. If such pathways occurred rarely, the congenital nature of the Wolff-Parkinson-White syndrome could probably

be established. As yet, reports of such studies have not been forthcoming, but three necropsy reports on cases exhibiting this syndrome have demonstrated anomalous communications between the atria and ventricles, offering support to the hypothesis of congenital origin of this syndrome.

General Comment

Five cases with disturbance of cardiac rhythm or conduction have been observed with congenital cardiac disease. In two, associated congenital cardiac anomalies were confirmed at necropsy. In one of these the congenital cardiac anomaly was a ventricular septal defect with a vascular ring surrounding the esophagus and trachea. In this case, acquired complete heart block was observed. Death was the direct result of the cardiac conduction disturbance. The next case studied at necropsy revealed infantile coarctation of the aorta. In this case an acquired arrhythmia diagnosed as supraventricular tachycardia was a contributing factor in the death of the infant. In one case of this series, although not studied at necropsy, unmistakable evidence of congenital cardiac disease existed. The probable diagnosis of Eisenmenger's complex was made. The development of supraventricular tachycardia in this case was a serious complication and one which could have been fatal. In three cases of the series, acquired ectopic cardiac rhythms or cardiac conduction disturbance developed in association with congenital cardiac anomalies.

In two cases of this series the only demonstrable evidence of congenital cardiac disease was the arrhythmia. In one of these, paroxysmal tachycardia in association with Wolff-Parkinson-White syndrome was observed. The arrhythmia was considered to be of congenital origin, in view of the age of the infant at the time the arrhythmia developed. Further support of the congenital origin of this arrhythmia is offered by the three recorded cases of this syndrome studied at necropsy. In the case of nodal rhythm reported herein, the ectopic rhythm was the only evidence of congenital cardiac disease. The nodal tachycardia was first diagnosed shortly after birth, but rapid fetal heart sounds had been observed in prenatal life. While an acquired lesion in utero cannot be eliminated, this case of nodal tachycardia is considered of probable congenital origin.

Although disturbances of cardiac rhythms and conduction have been recorded relatively infrequently in congenital cardiac disease, they constitute an important aspect of the problem. In two of the five cases of this series, the arrhythmia or cardiac conduction disturbance contributed directly to the death of the patient. In a third case the ectopic rhythm produced cardiac failure which was severe. In two of the five cases the ectopic rhythm was the only demonstrable evidence of congenital cardiac disease. In three of the cases discussed, disturbances of cardiac rhythm and conduction were considered acquired in the presence of congenital cardiac disease.

Summary

Five cases of disturbance of cardiac rhythm or conduction have been discussed. In three cases of ectopic rhythms (two cases of supraventricular tachycardia and one case of complete heart block), the cardiac disturbance of rhythm or conduction proved to be acquired in the presence of the following respective congenital cardiac anomalies: probable Eisenmenger's complex, ventricular septal defect and infantile coarctation of the aorta. In two cases with arrhythmias (nodal tachycardia and paroxysmal tachycardia with Wolff-Parkinson-White syndrome), the probable congenital origin is discussed. Routine electrocardiographic studies in infants and in congenital cardiac disease would probably reveal more frequent evidence of disturbances of cardiac rhythm and conduction associated with congenital cardiac anomalies.

Addendum

Personal communication from Dr. Henry A. Christian [30] was of considerable interest in Case 2 of this report. Dr. Christian wrote the author as follows: "Your case report in May, 1951, *American Heart Journal*, of Congenital Ventricular Septal Defect with Acquired Complete Heart Block has interested me much, as many years ago, to be exact some time between 1895 and 1897 when I was in charge of clinical work at the Massachusetts General Hospital I observed a young woman with the physical signs of a septal defect, who went into a complete heart block on two observed occasions as a sequence of cardiac decompensation. On the first occasion returning to normal rhythm when decompensation was ended by digitalis, bed rest and on the second occasion decompensation ended in death. I studied her with a home made polygraph and found evidence of complete block in the venous neck tracing.

"Autopsy showed uncomplicated defect of intraventricular septum high up and of large size in a hypertrophied heart. The His bundle seemed to run in the lower margin of the defect and showed no fibrosis or degeneration. I thought that with cardiac decompensation the dilatation of the heart dilated the septal defect and brought a temporary pressure on His bundle and consequent heart block. I never reported this observation."

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THE PSYCHE AND THE SOMA: THE SPIRITUAL AND PHYSICAL ATTRIBUTES OF THE HEART*

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Introduction

Psychosomatic medicine is "as old as the hills," or at least as old as the earliest humans who came down from the hills to establish civilized communities in the valleys and plains. The effect of "mind over matter" was the belief of our primitive ancestors as far as health and disease were concerned. There were no bacteria for them, or lesions of the brain or nerves or viscera, but evil spirits that had to be exorcised by extensive ritual in the hands of the witch doctors, of the magician and, finally, of the priest. Even Christ cast out devils to cure victims of mental disorders nearly 2,000 years ago. Medicine through the Dark and Middle Ages continued to be almost entirely psychosomatic. There was an art but not a science of medicine, despite the brilliant, though brief, illumination afforded by a few leaders such as Hippocrates and Galen during the 2,000 years that separated the institution of the school at Kos from the teaching at the great universities in northern Italy. It is of much interest that very early in the Eighteenth Century, actually in 1707, there was published in Rome a book entitled *Sudden Death,* by Lancisi, physician to Pope Clement XI, to whom the volume is dedicated. This book was printed to demonstrate the finding at autopsy of natural causes, mostly cardiovascular, of sudden deaths that had worried the Roman citizens, who were superstitiously fearful that God was displeased with them.

Even early in my own day the old practices of our superstitious ancestors had not entirely died out. My father in his general practice made liberal and apparently effective use of sugar pills of many hues with which we used to play doctor in his office at home when he was out. He permitted this game of ours with the brightly colored pills, but he was careful to place his potent drugs on the top shelves where we could not reach them. We cured ourselves of many imaginary ills, but we knew that when we were sick with fevers or upset stomach, sugar pills were ineffective. Not much else was truly effective in those days, either, except for rest in bed and nursing care and patience, aside from a very few specific remedies like antitoxin for diphtheria. If we waited a few hours or a few days or, in the case of typhoid fever, a few weeks, we would usually get well anyway, and it is of course that tendency for the young human constitution to recover from nearly every illness that largely sustained the reputation of the practitioners of medicine before the recent years of truly amazing progress in curative and

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preventive medicine and surgery. I know of one old country doctor who, years ago, had a considerable local renown in his pediatric practice based on this resiliency of the youthful human frame.

Even in our own day there exists an anachronistic survival of the primitive practices of the witch doctor, and it will be of interest to see how long in the future such may persist. It of course reflects somewhat the inadequacies of our own so-called scientific medical practice. I refer, as you may have guessed, to Christian Science. As a matter of fact, I myself had an early experience with this cult. Father, whose patients and their families did not need the services of Christian Science healers, nevertheless hired to help take care of us children, as a nurse, a Christian Scientist who incidentally on occasion sought his medical advice. She was a delightful motherly soul and quite expert in the care of children, which was, of course, the reason for her employment. One of my earliest memories as a very small boy was a trip she and I took, I expect by horse car, from the suburb of Roxbury, where we lived, into the city of Boston to attend a service at the Mother Church and to pay a call on Mother Eddy herself in her study after the service. She sat in state at one end of the room to receive her followers and is said to have given me her blessing when I was brought before her.

For many centuries in ancient days and during the Dark and Middle Ages, and even after the actual discovery of heart disease itself about the year 1500, symptoms and signs of illness were ascribed to disorders of the four humors, which were closely connected with the mental condition of the patient and which remain as expressions today largely to denote states of mind: (1) sanguine, from the warm moist blood; (2) phlegmatic, from the cold moist mucus; and bilious of two types: (3) yellow from the liver, warm and dry, favoring boldness and a good digestion, and (4) black, from the spleen, cold and dry, leading in excess to envy and melancholy (which means literally *black bile*).

Before the days of autopsies, at the turn of the Fifteenth Century when organic disease was first discovered as a common condition of the human body, it was natural that the mental attitude and attempts to influence it should hold almost the complete limelight. To be sure, the care of obvious external wounds and the use of certain medicinal plants, animals and minerals were currently employed, more as adjuvants to help the laying on of hands or the prayers for the sick one than as specifics in their own right. At this time, medical examination consisted in the main of urinoscopy and of the feeling and intricate description of the pulse, following the old Galenic doctrine of its variations according to the humors.

Finally, however, by the year 1800, organic heart disease had been so commonly encountered that Corvisart, Napoleon's physician, considered it commoner than all other diseases combined and the cause of nearly all symptoms and signs. Thus the pendulum had swung over the whole way,

and now medicine had become somatopsychic. It required a good many workers during the next hundred years to counteract this exaggerated doctrine. So far as the heart is concerned, it was in particular John C. Williams, who in 1836 wrote a book entitled *Practical Observations on Nervous and Sympathetic Palpitation of the Heart, Particularly as Distinguished from Palpitation, The Result of Organic Disease,* in which he begged his colleagues in medicine and surgery to accept again some of the older ideas that all symptoms, especially of cardiac nature, were not due to organic structural disease. Slowly and painfully the pendulum swung back again. But once more, in our own time, there has been a revival of a tendency to overemphasis of the psyche over the soma, with the introduction of the term "psychosomatic medicine," which under other designations is, as I said at the beginning of this discourse, as old as the hills.

Neither the psyche nor the soma should hold the limelight. They comprise but halves of the same circle, without beginning or end but with varying, alternating or even coincidental lengths of arc. We cannot well consider them separately. We must put the body together again, and I would like, in the time remaining to me, to refer to the relationships of psyche and soma from the standpoint of the heart and its diseases.

The Effect of the Psyche on the Soma

The effect of the mind and its emotions on the circulation, which includes both the heart and arteries, has been recognized, since the earliest days. This is true both in health and in disease. Commonly there is an elevation of the pulse rate and of the blood pressure as a result of sympathetic stimulation, with or without coincident vagal release. Such an effect may give rise to uncomfortable palpitation in hypersensitive individuals, and associated with such palpitation there may be actual pain, consisting of heartache and sometimes precordial soreness. Emotional stimulation, as from fear, does rarely cause primarily a vagal effect, with slowing of the heart or even actual syncope due either to standstill of the heart, drop in pressure, or both combined. The alarm reaction, which has created great interest during the past few years as propounded by Selye on the early work of Cannon, apparently can be more far reaching than the transient effect of excitement on the heart rate and blood pressure. The mobilization of adrenalin and subsequent secondary endocrine effects may very well explain some chronic and finally permanent changes that occur as the result of the nonspecific alarm reaction from various noxious agents. Thus chemical and eventually structural changes in the body can occur in the defense reaction if prolonged or frequently recurrent. Whether such diseases as hypertension can be so explained we do not yet know, but there is accumulating evidence that certain conditions, such as changes in the connective tissues (the collagen diseases), with the production particularly of arthritis—for example, rheumatoid—and of rheumatic fever, may be de-

pendent on disturbances of hormonal nature, as indicated by the recent dramatic correction, temporary at least, of these conditions by adrenocorticotropic hormone (ACTH) and cortisone. Thus we are apparently on the verge of important new information about the relationship of the psyche to the soma. I recently wrote to Dr. Selye to learn of his latest experience or knowledge about the effect of emotional strains per se in contrast to other factors in the full development of the alarm reaction resulting in bodily changes. He replied as follows:

"In reply to your letter of November 9th, let me say that we are now giving especial attention to emotional and other nervous stimuli as agents eliciting the general-adaptation-syndrome.

"The main facts which have become obvious so far are that nervous stimuli are far more potent than most other agents in eliciting this syndrome. They do so even under conditions which can hardly be described as causing somatic damage.

"My pupil, Dr. Fortier, finds among other things that intense light or sound elicits the adrenal changes characteristic of the alarm reaction (loss of ascorbic acid and cholesterol) within 15 to 30 minutes. Following exposure to light, such responses are not seen if the eyeballs are removed, hence, the effect is certainly due to light itself and not to heat or any invisible radiation."

It is quite clear, as the result of observations during the past few decades, that *cardiac enlargement, permanent arrhythmia and even heart failure may on rare occasions develop in an otherwise perfectly normal heart following prolonged or recurrent excessive tachycardia of abnormal nature,* as in the case of paroxysmal or permanent auricular fibrillation or flutter and prolonged auricular tachycardias. It has been the tendency sometimes in the past to ascribe auricular fibrillation to structural heart disease, and although it is quite certain that the majority of patients who show auricular fibrillation do have antecedent organic heart disease, such as mitral stenosis, there are instances of individuals with perfectly normal hearts to start with who are troubled by auricular fibrillation apparently set off by nervous influence. It is true that arrhythmias occur more commonly in older persons and tend to increase with increasing age, but there need be no discoverable structural change in heart muscle or valves in patients with auricular fibrillation or auricular flutter, and I myself have followed many individuals who have remained in good health for years after one or two ancient attacks of paroxysmal arrhythmia of this nature. They are now acceptable for life insurance as they were not years ago. Thus the presence of auricular fibrillation in a man or woman aged 55 does not mean that we should make a diagnosis of arteriosclerotic or coronary heart disease, as was once done. The point that I want to raise now is that, although one may find disturbances of rhythm in the form of extreme tachycardia in the case of otherwise

perfectly normal hearts, tachycardia may, in some individuals at least, lead eventually to enlargement, permanent arrhythmias, and finally heart failure such as formerly resulted from a severe chronic thyrotoxicosis.

A 55 year old man for many years had prolonged paroxysms of tachycardia, regular at first, but eventually consisting of auricular fibrillation. The attacks would last for hours on end and were not controlled by any of the procedures customarily used, or at least were controlled only with great difficulty. Eventually cardiac enlargement developed and with it, finally, permanent auricular fibrillation and congestive failure. With the usual remedies employed to combat congestive failure, a fair degree of health was maintained for a few years prior to death resulting primarily from the congestive failure. Autopsy showed no evidence of valvular disease or important coronary atherosclerosis. There had never been hypertension, but the heart was heavy, both ventricles being dilated and somewhat enlarged. This was an instance of the development of heart disease from a functional disorder which at the beginning had been induced by emotional stimuli.

Another case, Miss E. S., a 39 year old bookkeeper, consulted us nearly three years ago because for four years she had had frequent spells of rapid heart action, sometimes regular and sometimes irregular, due to either auricular paroxysmal tachycardia or auricular fibrillation. During the previous year she had had an increasing number of attacks, so that a day rarely went by without them, and she became semi-incapacitated. There was no known aggravating factor except nervous strains. She smoked 10 cigarettes a day. Between attacks she felt perfectly well.

Physical examination showed no abnormality except for arrhythmia at the time of an attack. There was no murmur. The blood pressure was normal. There was no evidence of congestive failure. The roentgen-ray examination showed definite though not marked enlargement of the heart. Bilateral thoracic sympathectomy was carried out with apparently beneficial results, and she has been definitely improved during the past year. My last note, made on September 20, 1949, included the following comment: "General health good. No evidence of heart disease except for the slight cardiac enlargement which probably originated from the intractable tachycardia of by-gone days. The arrhythmia nowadays is not especially troublesome and does not interfere with her program."

Actual cardiac enlargement of important degree or heart failure, however, is rarely caused by abnormal rhythms which may be set off by emotional strain. Such cases constitute certainly less than 1 per cent of all heart disease, but they do occur. *Still rarer is death due to the effect of emotion on the circulation in a person with a healthy heart.* However, even this is a possibility. One case cited some years ago by Dr. Martland is an example of the possibility, distinctly remote, of death by cardiac standstill or by ventricular fibrillation in a healthy person, the only such among his 2,000 autopsies after sudden death. This particular instance was that of a young

Negro who came to a hospital clinic because of a slight skin lesion on the face. He wished to have this removed by the application of some ointment, but he was advised that it should be removed by excision under local anesthesia. He objected and showed a good deal of apprehension about such therapy, but he was finally persuaded to have this minor operation carried out. However, even before procaine was actually injected and before the needle had quite punctured his skin, the man fell forward dead. Autopsy showed no evidence whatsoever of organic heart disease or any other disease. This case may be cited as an example of the exception that proves the general rule that emotion is not likely to cause sudden death in a healthy person.

Much more important and common, however, is the effect of emotions on individuals who already have heart disease. In such individuals, arrhythmia, heart failure particularly, as indicated by acute pulmonary edema, angina pectoris, perhaps acute coronary thrombosis followed by myocardial infarction, and even sudden death may result from what may seem a minor nervous or emotional strain. Effort is the commonest immediate exciting cause of angina pectoris in a person who has a faulty coronary circulation. An overfull stomach is sometimes a factor too, especially the combination of effort and a recent meal, but almost as common as effort behind the production of angina pectoris is excitement. Fear, great pleasure, anger, and the excitement of an athletic contest, such as viewing a football game or boxing match, directly or by television, or even listening to one over the radio, have caused innumerable deaths in patients with serious heart disease, especially in those with coronary insufficiency. One of the rules in treatment that we have advised for many years is that such patients avoid nervous strain as much as physical strain, and especially various combinations, as, for example, rapid walking on a cold evening right after a hearty meal and in an excited frame of mind. Such coronary deaths usually come through the introduction of ventricular fibrillation secondary to the added strain of an increase of pulse rate and blood pressure in a heart that cannot stand such strain. Before leaving this aspect of the subject, one should mention peripheral circulatory reactions as well as those of the heart itself. Raynaud's syndrome, with the blanching and pain in the fingers, is readily brought on in a person subject to such trouble by excitement as well as by cold.

The Effect of the Soma on the Psyche

Of equal importance to the effect of the psyche on the soma is the influence of disease of the heart and blood vessels on the mental state. The experienced physician, realizing this, includes in the treatment of his cardiovascular patients the most careful consideration of the mental reaction to the announcement of what he finds wrong. A careful discussion with the family at the earliest possible time, and with the patient after early childhood, as to what is found wrong is perhaps the most essential part of the study and treatment that will follow during the rest of the patient's life. Awkwardness

and inexperience in the handling of patients in the early stage of their illness may lead to serious trouble, in the form of psychoneurosis, depression, lack of coöperation in the essential treatment, and distrust of the medical profession. The cults, including Christian Science, have in large measure thrived as the result of our ineptitude in this particular. I would like to cite the effect of certain circulatory conditions on the mental state or psyche, but before doing so I should mention the fact, well known of course, that heart and vascular disease themselves, particularly myocardial and cerebral arteriosclerosis and renal insufficiency, may directly affect the circulation in the brain and alter the mental state. With these effects I am not concerned at the moment, aside from recognizing their existence, although on occasion they may be very important. Sometimes medicines given in the treatment of cardiac patients may be responsible for disorders of the mind. Digitalis probably does not fall into this category, but bromides used on occasion to quiet patients, morphine to which the patient may become habituated, and certain other drugs may have an unfavorable effect. Incidentally, an exhausting insomnia may result from a poorly recognized orthopnea due to heart failure, and may be cleared by appropriate treatment of the congestion and not by hypnotics per se.

The commonest influence of the soma on the psyche is the simple *fear of heart disease,* even in its absence. In this day and age, when newspapers and radio announcements are full of reports of deaths from heart disease and when an individual is impressed by the number of such events, especially among his friends, relatives or acquaintances, and when on occasion he himself feels a little palpitation due to extrasystoles or nervous tachycardia, he may develop an important neurosis which needs to be quickly dispelled by his physician, sympathetically and firmly, and not with derision. Sometimes the fear of heart disease is aggravated by the actual presence of symptoms of neurocirculatory asthenia or the so-called anxiety neurosis. Here there are multiple symptoms in the form of heartache, shortness of breath, often of the sighing variety, palpitation and faintness. Neurocirculatory asthenia is not to be disregarded or considered purely as fear. It is a disorder not yet understood or clearly explained, which very probably has some basis in disturbed body function, chemical or otherwise. Neurocirculatory asthenia is frequently superimposed on actual structural heart disease, and here there is, of course, the added difficult problem of differentiating between the two and of treating both conditions in the best possible way.

Disorders of ***rhythm,*** which may sometimes be set off by emotions, may in turn cause great mental distress and on occasion have been responsible for serious neuroses and sometimes even for morphinism. Much reassurance and sympathetic but adequate treatment should be carried out for such disorders of rhythm. An example of the distress that may occur to both patient and family is found in the following instance.

A middle-aged woman living in the Southwest had for some years been

bothered by paroxysmal tachycardia, lasting on occasion up to a few hours, not adequately controlled by various medical measures which had been tried. Because she sometimes felt faint with these attacks and because they stopped more quickly if she lay down to rest, she had become accustomed to stop whatever she was doing in order to seek such refuge. Inasmuch as the attacks were becoming more frequent, occurring sometimes several times a day, and inasmuch as the family were greatly alarmed because of "mother's heart spells," she had ceased to mention them to her family and friends when they came and would carry on actively whatever she was doing. She was much troubled during such times both by the discomfort of the palpitation and by some faintness, and the attacks, as a result, would last longer. Finally, she decided to seek further advice and came with her family to Boston for consultation. We found no evidence of heart disease. She was in general a healthy woman but much troubled by two things: chiefly, the apprehension of her family, and secondly, her own discomfort during the attacks. The treatment needed was obvious: it consisted in large part of reassurance of the family, who were told that it was not necessary for them to be alarmed by the attacks, and that she should be allowed to rest quietly in order to shorten them. This, plus further use of quinidine, cleared up the problem.

Enlargement of the heart is a diagnosis that sometimes strikes fear in a person who has rightly or wrongly had such a diagnosis made, by physical examination, roentgen-ray evidence or electrocardiography. The range of the size of the normal heart is so great that such a diagnosis should be made only with the greatest caution. It is better to make an error of omission than commission in this respect, because borderline or slight enlargement of the heart without associated troubles can usually be disregarded except as one would recommend periodic follow-up examinations. Even a moderately large heart may allow survival for a good many years. A very large heart however is of course a sign of great strain, past or present, and has in general a poor prognosis, although there are exceptions here too.

Murmurs may excite great concern and should be carefully analyzed as to site, intensity and timing. Patients should be told that many murmurs are normal, the results of physiologic processes. It is really surprising that murmurs are not found in every heart normally. They can generally be induced in everyone in the pulmonary valve area on full expiration in the recumbent position, especially in a young person. Even a loud murmur, there being no other important findings, may be minimized, although its presence should always be acknowledged and follow-up examinations advised.

Most common of all, as causes of serious cardiac neurosis and sometimes unnecessary crippling of lives, are the two conditions of *hypertension* and *coronary heart disease*. It should be remembered that some elevation of blood pressure above the usual normal is very common, and in only a relatively small percentage of individuals so affected is the condition serious or

life appreciably limited in activity or duration. In a recent survey of some 2,000 cases with hypertension in New York City, only 5 per cent were found to be malignant in variety. Thus, for the great majority of patients with hypertension no radical measures are needed. Reassurance and simple advice to maintain proper weight and avoid undue nervous strain and tobacco are in order. The overemphasis on hypertension which has come in our day, due to its frequency and publicity and the development of radical therapeutic measures, as yet not specific, has resulted in a great deal of unnecessary apprehension, and this very apprehension in its turn increases the blood pressure at the time of any examination.

An example of this problem is that of a woman 57 years of age who was referred to me last winter because of the finding of symptomless hypertension and her considerable concern about it. Physical examination, roentgen-ray film and electrocardiogram showed no abnormality except for hypertension of variable degree, averaging about 190 systolic and 105 diastolic, rising to higher levels when nervous, but much of the time settling to lower levels with sedation and reassurance. She doubtless represents a large group, particularly of older women, who carry hypertension of variable degree for many years without harm. If such persons, by keeping their weight down and avoiding excessive stimulation and fatigue, can maintain most of the time a pressure that is not unduly high—that is, not appreciably over 180 systolic and 100 diastolic—there is no need of measures of radical treatment. The actual taking of the blood pressure itself is probably one of the greatest pressor agents of all.

Coronary heart disease is perhaps the most mentally crippling of all diagnoses. The dread terms "angina pectoris" and "coronary thrombosis" have struck fear into the hearts of innumerable individuals during the last few decades. Now, fortunately, there is a healthier attitude, based on the frequency of minor and often simply temporary illness due either to angina pectoris of effort or to acute myocardial infarction, with good recovery therefrom. To be sure, coronary heart disease continues, apparently in increasing degree, to be one of the most important threats to the health of this country, and much serious research is needed to reduce its incidence, especially in middle-aged men in business and professional life, but the actual number of cases of coronary heart disease who are seriously crippled is relatively slight, probably not much more than just referred to for hypertension. In my own experience, angina pectoris and myocardial infarction are so common that I have come to consider them as almost normal events in the life of the average American male. Many times have I followed patients who are perfectly well 10, 15 and 20 years after having been temporarily incapacitated by angina pectoris and coronary thrombosis. Perhaps the most difficult aspect of important coronary heart disease in the typical victim—that is, the active middle-aged man—is that he is struck down for at least a few weeks or months at the height of an extremely active career. This

tends to shatter his morale. The treatment must be most carefully directed at the start to maintain a proper mental outlook, with favorable prognosis possible as a rule. Optimism is here generally justified, and when it is possible to be optimistic this attitude itself helps greatly in the recovery.

Several years ago a business man who was also a golfer of considerable ability came to see me at the age of 55, complaining that he was no longer able to play golf or to walk rapidly in the morning to the train because of a feeling of substernal tightness. He was very much discouraged because he believed that from that moment on he would be crippled and would not live long. He was especially distressed by having to give up golf. Examination revealed very little in the way of objective abnormalities. The electrocardiogram was essentially normal, but the diagnosis of coronary heart disease with angina pectoris was clearcut. He was advised to limit his activity as needed for the next few months, to use nitroglycerine as required, but to be hopeful about the future. He was very mistrustful of this advice and believed that we were unduly optimistic. After another few months, which carried him through the winter, he reported much improvement, and by summer was able to resume golf without medication at all, something he had not dreamed possible the previous fall. He has since continued in good health and plays golf regularly. This is an illustration of the justification of optimism in so many of our cases, based on the common development of an adequate collateral circulation in the face of slight to moderate coronary insufficiency due to coronary atherosclerosis, the insufficiency being a manifestation which often passes.

Another old patient of mine I have seen again recently, 22 years after severe acute myocardial infarction due to coronary thrombosis at the age of 57, at which time his family were warned of the possibility of death during the acute illness and of a crippled life thereafter. I found this man, a physician, in fairly good health. When I saw him in consultation 22 years ago, I advised against his retirement at least until a few weeks or months had passed. He improved sufficiently to be able to carry on his work until he reached the age of retirement, and since then he has continued to do useful work three times a week as a consultant at the age of 79. He is troubled somewhat by intermittent claudication and less by slight limitation of his coronary reserve. Such an instance as this doctor patient can be multiplied many times over.

The relationship of these various types of cardiovascular disease to the psyche has many aspects which may be mentioned but do not need to be stressed. This applies to the life of children at school, to their engagement in sports, to marriage and child-bearing, and to occupations. One cannot establish any hard and fast rules for the effect of any of these disease conditions on any of these phases of life. One must individualize in every case with reference to the degree of heart disease, the attitude and experience of the patient, his intelligence and his mental state; but we have now entered

a period in medical history in this country with emphasis on the chronic diseases, particularly of the circulation, where much more attention must necessarily be paid, in the aging population to the effect of cardiovascular disease and disorders on the psyche, that is, on the mind and on the morale.

The Psychosomatic Circle

I stressed in my introductory remarks the importance of recognizing the unending relationship of the psyche and the soma, that is, of the mind and of bodily changes. We must make every effort to improve not only the bodily health but also the mental outlook of our patients, because of the certainty that either may act favorably or unfavorably on the other. Sometimes there is a vicious circle which we can break. It can still be a circle, but a beneficent one and not harmful. Thus there seems to be little or no point in medical practice, except in the serious, difficult or refractory cases, in overemphasizing the treatment of either the psyche or the soma. On occasion, surgical therapy as an example of purely physical treatment may effect a cure that will have a favorable influence on mental health. Examples of this are resection of a constricting pericardium, the reduction of blood pressure and heart strain in hypertension by lumbodorsal sympathectomy in suitable cases, and surgical amelioration of the tetralogy of Fallot, but the majority of cardiovascular cases need no such radical treatment. Similarly, only rarely is the most specialized psychotherapy needed, even in cases with a considerable degree of established psychoneurosis. Exceptions certainly exist, but the practicing physician at large can himself handle, as a rule simultaneously and without too much detailed distinction, both body and mind in his treatment of disease.

The Importance of the Spiritual Attributes of the Heart

The psyche may be translated in two ways: first, as mind, and second, as spirit; but there should be a distinction between the two. The mind manufactures thoughts which may or may not be spiritual; the spirit is a particular possession of mankind, distinguishing him from the lower animals and distinguishing leaders throughout the ages from those constantly engrossed in mundane matters, although there is at least a spark of spirit in all human beings. The soma, and that part of the psyche which is the mind, are mortal; the spirit lives, as Vesalius wrote on the pedestal shown on Van-Calcar's woodcut of the skeleton that leans against it: "The spirit lives, all else is mortal." The spirit can be passed on by any individual during his life and can be handed on through his inspiration at his death. We physicians have the opportunity of inspiring our patients with courage, determination, optimism, equanimity and patience, all attributes of the spirit. The word "courage" comes from the word "heart"—"coeur" in French, "cor" in Latin; and it is courage above all things which is needed by many

individuals who have cardiovascular disease. Such virtues as courage, optimism and patience may neutralize, somewhat at least, the effects of the alarm reaction, acute or chronic.

We need to analyze more than we have yet done the physical effect of the influence of these positive virtues. We have paid perhaps undue attention to the reverse, that is, to the harmful effects of fear, sorrow and anger. It is quite certain that biologic effects also result from cheerfulness, optimism, courage and joy. A chance to counteract the harmful effects of pain, sorrow and anger is possible through the inculcation of a happy disposition, which can be acquired as well as inherited. We know that clinically there are definite effects from the application of this idea. Helpful psychotherapy and the best practice of medicine depend on it in considerable part. It is probably the basis of the success of the magic temple rites in some of the treatment of the past, and also of the present popularity of such a relic as Christian Science. This situation reminds me of the current habit of the daily press of headlining and emphasizing the bad things that take place—the fires, murders, robberies, wars and deaths—while much too little attention is paid to the good things that go on every day, every week, every month and every year. So it seems to be in our medical writings—almost everything is concerned with disease; too little is concerned with the maintenance of good health, including the establishment of good habits, of which the cultivation of the spiritual virtues of courage, optimism and useful industry forms a part.

Many of the best things that have come to the world in its history have resulted from the courage and good works of physical cripples, persons who are crippled in limb or sight or hearing or by internal diseases. Since heart disease is one of the most common of all, the accomplishments of cardiac cripples constitute one of the happiest and most stimulating experiences of my professional career. Time after time, patients of mine have transcended their ills, and that very act of theirs has improved their health and prolonged their lives. Of course, common sense and good advice are necessary corollaries to these accomplishments, but the spirit is often a major factor. This may, of course, be largely inborn, but I am certain that it can be contagious and transmitted.

Before I give a few examples of such spiritual attributes of the hearts of some of my patients, I would like to quote from an ancient writing deploring the overemphasis of the detailed care of one's health that has been so common all through the centuries and that still enters into the conversation of so many people who are either well or sick. Plato wrote in the Fourth Century B. C.: "Not so extraordinary, I replied, if you bear in mind that in former days, as is commonly said, before the time of Herodicus, the guild of Asklepios did not practice our present system of medicine, which may be said to educate diseases. But Herodicus, being a trainer, and himself of a sickly constitution, by a combination of training and doctoring found out a

way of torturing first and chiefly himself, and secondly the rest of the world . . . by the invention of lingering death; for he had a mortal disease which he perpetually tended, and as recovery was out of the question, he passed his entire life as a valetudinarian; he could do nothing but attend upon himself, and he was in constant torment whenever he departed in anything from his usual regimen, and so dying hard, by the help of science he struggled on to old age.

"A rare reward of his skill."

And from Sir William Osler: "Asklepios did not instruct his descendants in valetudinarian arts, because in well-ordered states individuals with occupations had no time to be ill. If a carpenter falls sick, he asks the doctor for a rough and ready cure—an emetic, or a purge, or a cautery, or the knife—these are his remedies. Should any one prescribe for him a course of dietetics and tell him to swathe and swaddle his head, and all that sort of thing, he says 'he sees no good in a life spent in nursing his disease to the neglect of his customary employment; and therefore bidding good-bye to this sort of physician, he resumes his ordinary habits, and either gets well and lives and does his business, or if his constitution fails, he dies and has no more trouble.' "

And Celsus, soon after the beginning of the Christian era, said:

"A man in health, who is both vigorous and his own master, should be under no obligatory rules, and have no need, either for a medical attendant, or for a rubber and anointer. His kind of life should afford him variety; he should be now in the country, now in town, and more often about the farm; he should sail, hunt, rest sometimes, but more often take exercise; for whilst inaction weakens the body, work strengthens it; the former brings on premature old age, the latter prolongs youth.

"It is well also at times to go to the bath, at times to make use of cold waters; to undergo sometimes inunction, sometimes to neglect the same; to avoid no kind of food in common use; to attend at times a banquet, at times to hold aloof; to eat more than sufficient at one time, at another no more; to take food twice rather than once [or as now thrice] a day, and always as much as one wants, provided one digest it." And he said further: "It is well to recognize, that all branches of medicine are so connected together, that it is impossible to separate off any one part completely."

One of the leading American composers was a victim of the tetralogy of Fallot, and his early medical advisors believed him doomed to die in childhood or early adult life. Even a proper education was withheld from him because of the waste of money that it was thought would result. He was cyanotic, his fingers were clubbed, he was short of breath, easily fatigued and faint, and yet with persistence and an extraordinarily dogged courage he obtained his own education and even worked his way in some capacity or other on a cattle boat to Europe to study music in Paris. His name was Henry Gilbert. At the age of about 55, having already outlived his life

expectancy by many years, he went to Europe and took part in musical festivals given on the continent in his honor. He returned to this country and continued actively in his work until his death in his sixtieth year.

Another patient of mine, also cyanotic and with clubbing of the fingers since early childhood, carried on a happy and useful life as secretary and librarian almost to the end of her life, when she finally died at nearly 75 of right heart failure secondary to a combination of a very severe degree of pulmonary stenosis with an auricular septal defect. She too broke the world's record, and by some 18 years.

It isn't just because of longevity that I mention these two individuals, but because of what they accomplished despite their heart trouble. It was obvious in each case that encouragement by physicians played a helpful rôle in their careers.

Two other patients of mine I would briefly mention. One, a school teacher with very severe rheumatic heart disease, consisting of mitral stenosis, auricular fibrillation and very limited myocardial reserve, continued to teach many years after it was thought necessary that she resign. She lived, to be sure, a very guarded life, going back and forth from her home to school by taxi each day, and remaining at rest in bed or chair whenever she was not in school. She was an able teacher and a very important citizen, a source of wonder, admiration and inspiration to her fellow citizens.

The other, a woman I saw many years ago, was a cripple because of her easy fatigability in the presence of a considerable degree of rheumatic heart disease. As the events in her life unfolded, it became necessary for her to leave her husband and to take over the entire care and support of herself and her children. This challenge changed her life. She developed an extraordinarily courageous attitude, and for years has carried on actively in useful work which has afforded her sufficient income. She has written the story of her life as an encouragement to other women similarly placed.

Finally, I would speak of a prominent official, a minister from a distant country, a man long ill with hypertension and some of its effects who, because of his importance in bringing help to his country and the rest of the world in this critical period of history, accepted the sacrifice of a very arduous position. This was at first strongly against his wish and plans for his future health. Suddenly, however, he developed a new philosophy of life, and once he had accepted this rôle of sacrifice in a calm and dispassionate way, his health improved. He no longer had any fear or apprehension, and has ceased to have some of his symptoms; although still a sick man, he has carried on astonishingly well.

These cases I have cited are instances of the favorable effect that the inheritance and inculcation of the virtues of the spirit may have on the soma and the physical health of the individual. I am sure that this fact can be illustrated thousands and thousands of times by innumerable physicians. Yet too little of this is appreciated in general or stated in particular.

I have spoken of cardiovascular disease because that has been my chief interest, but what I have said applies equally well to many other fields of medicine. In closing, I would emphasize once more what I discussed before the Massachusetts Medical Society last spring in a lecture, entitled "La médecine du coeur," which, freely translated, means "medicine from the heart": a friendly, beneficent attitude of physician towards his patients, in relation to his community, to problems of national health and to international relations. This will do more than anything else to make it unnecessary in future medical discussions to separate the psyche from the soma or to overemphasize either one.

THE MECHANISM OF GALLOP SOUNDS, STUDIED WITH THE AID OF THE ELECTROKYMOGRAPH*

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It is generally agreed that gallop sounds are in some way related to the rapid filling of the ventricles during diastole, but the exact mechanism of their production is controversial. Potain,[1] Ohm,[2] Bridgman,[3] Wolferth and Margolies,[4] Orias and Braun-Menendez [5] and others believe that the sound is produced by an impact or a sudden distention of the ventricular wall, imparted by the rapid flow of blood into the ventricle during diastole. On the other hand, Gibson,[6] Hirschfelder,[7] Thayer,[8] Sewell,[9] Dock [10] and Lewis and Dock [11] believe that the extra cardiac sound is valvular in origin. Recently, Brady and Taubman [12] offer support for the theory of reflux closing of the auriculoventricular valves as the most likely mechanism for the production of protodiastolic gallop sound on the basis of electrokymographic and slit roentgenkymographic studies.

In the attempt further to elucidate the problem, this investigation was undertaken (1) to determine whether a consistently abnormal movement of the left ventricular border is present at the instant when the gallop sound occurs; (2) to study the nature of the left ventricular filling curve, and particularly its relationship to protodiastolic and presystolic gallop sounds, and (3) to compare and correlate the movements of the left ventricular border when a gallop sound is present with border movements when the gallop sound is absent, after digitalis administration, in repeated sequential studies in each of several individuals.

Material and Methods

Selection of Patients: The patients used for this study were selected from a large number of hypertensive individuals admitted for treatment to the Hypertension Clinic and Medical Wards of the Hospital of the University of Pennsylvania. Of the many patients with gallop rhythm, 28 were selected in whom the intensity of the gallop sound was thought sufficient for satisfactory recording. It was soon found impossible to obtain satisfactory sound and electrokymographic records simultaneously from all of these patients.

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After considerable experimentation and study, four hypertensive patients with gallop rhythm were chosen for detailed study for the following reasons:

1. They were slender and of asthenic habitus, without pleural effusions or extensive pulmonary congestion. Recordings of the feeble border movements of individuals with gallop rhythm were usually technically unsatisfactory in stocky or obese subjects, or in those in whom the cardiac border could not be clearly demarcated from the adjacent organs.

2. The gallop sounds were clearly audible with the subject sitting. This posture was desired because cardiac motions unrelated to changes in volume were less than in recumbency, and technically satisfactory tracings were much more readily obtained. Loud gallop sounds in recumbency disappeared in many individuals when they sat up.

3. Rhonchi, loud râles and other extraneous sounds were absent or insufficient to distort the sound records.

4. Subjects with myocardial infarction were excluded because of the resulting abnormality of border movements.[13-16]

5. They were willing and able to coöperate.

Two of the four patients had presystolic gallop rhythm, and one of these two patients also had mechanical alternans. The gallop sounds of the other two patients were of the protodiastolic type.

Method of Study: In each of the selected subjects, studies were deferred until the patient had been treated for heart failure with digitalis and other measures. This regularly resulted in disappearance of the gallop sounds. The first electrokymogram of the movements of the left ventricular border, together with simultaneous sound and electrocardiographic recordings, was made soon after cardiac compensation had been restored. Ballistocardiograms and recordings of venous pressure were also taken in conjunction with the study. Then, while the patient was kept under close observation, digitalis administration was temporarily interrupted. Gallop sounds of the intensity satisfactory for the purpose of recording were found to reappear in from 10 to 20 days following the withdrawal of digitalis therapy. Demonstrable peripheral edema, pulmonary congestion, pleural effusion or excessive dyspnea had not yet developed. Subjectively, some shortness of breath and palpitation with exertion had usually begun to appear. At this time electrokymographic, ballistocardiographic and venous pressure recordings were again made. Immediately after these studies were completed, digitalis and mercurial diuretics were again instituted to control the symptoms and signs of impending heart failure. In each of the four patients, digitalis was administered and withdrawn sequentially three or more separate times. The various graphic records and readings of venous pressure made during the period of cardiac compensation under digitalis effect, and those similarly recorded at the time when gallop sounds were prominent following the withdrawal of digitalis therapy were analyzed and compared.

Recording Material and Methods: The electrokymographic equipment used in this study is of the type developed by Henny, Boone and others [17, 18] and manufactured by the Cambridge Instrument Company. The time lag of this particular instrument has been calibrated at 0.015 second within a frequency range of 1 to 35 cycles per second. The simultaneous phonocardiographic, electrocardiographic and electrokymographic tracings were recorded with a Sanborn Tribeam instrument. The ballistocardiograms were taken in Dr. Isaac Starr's laboratory, using the table type ballistocardiograph.[19, 20]

Results

From the tracings taken upon the 28 patients, originally studied, it was clearly apparent that the configuration of the movements of left border was consistently abnormal. Otherwise, no specific information was gained which was not more clearly apparent from studies of the records of the four patients selected for detailed observations.

Presystolic Gallop Rhythm: The electrokymogram of the left ventricular border of each patient with presystolic gallop rhythm showed a characteristic abnormal pattern during three periods of digitalis administration, and a different abnormal pattern during three periods after the drug had been withdrawn. After digitalis had been withdrawn and gallop sounds had reappeared, these features were observed: (1) The ventricular filling curve

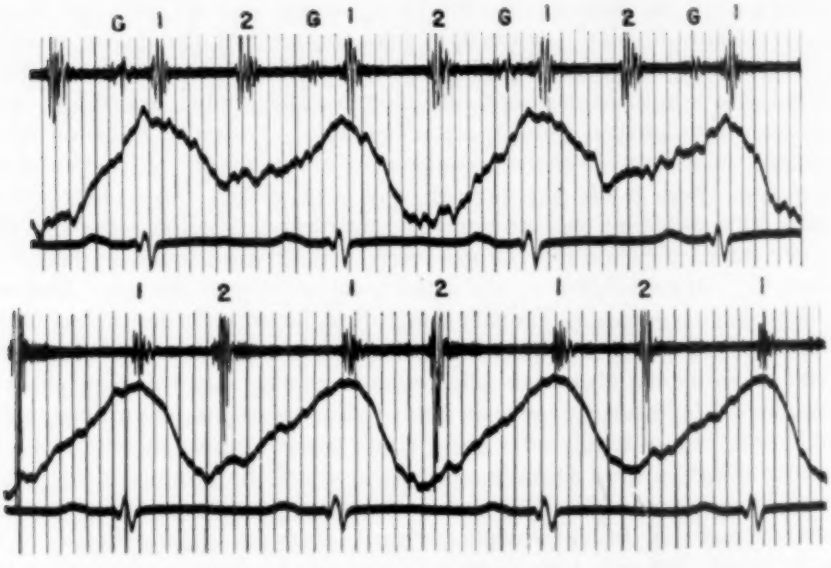

FIG. 1*a* (*above*). Presystolic gallop rhythm. Mechanical pulsus alternans. Gallop sounds (G) alternate in intensity. Each sound falls near the middle of the late diastolic rapid outward movement of the left ventricular border. *b* (*below*). Same subject after digitalis. The gallop sound and the presystolic rapid lateral left ventricular border motion have disappeared.

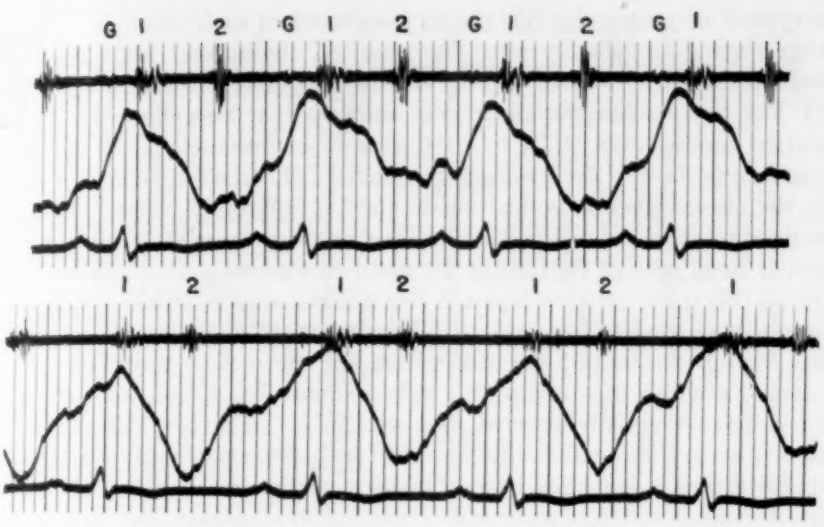

FIG. 2*a* (*above*). Presystolic gallop rhythm. Gallop sound during steep slope of outward movement of the left ventricular wall. *b* (*below*). Same subject after digitalis. The gallop sound and the presystolic rapid outward motion have disappeared.

ascended rapidly in late diastole, 0.10 to 0.12 second after the beginning of the P wave. (2) The peak of outward border movement occurred 0.04 to 0.06 second after the onset of the electrical systole, and 0.01 to 0.06 second before the initial vibrations of the first heart sound. (3) In every instance the gallop sound was observed to fall near the middle of the uprising limb of the curve, 0.04 to 0.06 second before reaching its peak (figures 1a, 2a). (4) In both patients, in tracings from the lower left ventricular border, a slurring or tendency to notching was often recorded in the descending limb of the curve, early in systole.

Within a few days of the institution of proper measures to combat heart failure, and with the disappearance of the gallop sounds, the kymograph reverted to its original appearance. It differed from the above in the following respects: (1) The sharp upswing of the curve in presystole was no longer observed. (2) The peak of the left ventricular outward movement was relatively delayed. It occurred during the first sound of the subsequent cardiac cycle, 0.06 to 0.10 second after the onset of the electrical systole. (3) The slurring or notching of the descending limb disappeared (figures 1b, 2b).

Protodiastolic Gallop Rhythm: As with patients with presystolic gallop rhythm, the two patients with protodiastolic gallop sounds each showed a characteristic abnormal electrokymographic pattern during three periods of digitalis administration and a different pattern during three periods after the drug had been withdrawn. During periods of digitalis withdrawal, movements of the left ventricular border revealed the following: (1) A sharp

rising limb of ventricular filling curve occurred in early diastole. This upswing began immediately after the onset of the second heart sound and continued rapidly upward to form a small toothlike projection at its peak. (2) The phonocardiographic tracing showed that the gallop sound always occurred immediately (0.01 to 0.04 second) before the peak of the steeply ascending portion of the kymographic curve. Thereafter, following a small dip, the curve either smoothed out to form a horizontal plateau throughout the remaining period of the diastole, or sloped gently upward again to form another small peak at the time of the first heart sound. (3) The descending limb of this more or less trapezoid-like pattern was inscribed by the mesial movement of the left ventricular wall during systole (figures 3a, 4a). This early rising, flat-topped electrokymographic curve was recorded in every instance in which a protodiastolic gallop sound was heard, not only in the two patients especially selected, but also in six others. Again, as in the cases of presystolic gallop rhythm, this very abnormal pattern assumed an entirely different but more normal looking configuration soon after digitalis administration and disappearance of the gallop sounds. The most striking change noted following digitalization was a shift of the peak of the rapid ventricular filling wave from relatively early in diastole to the time of the first heart sound in the subsequent cardiac cycle, 0.06 to 0.10 second after the onset of electrical systole (figures 3b, 4b).

Pulsus Alternans and Gallop Sounds: One of the patients with presystolic gallop rhythm had, at times, a prominent pulsus alternans. During one of the induced periods of gallop rhythm, alternation in the gallop sound and that in the ventricular filling curve were recorded simultaneously. The electrokymogram showed incomplete systolic emptying in every other heartbeat. On examining the sound tracing in correlation with the electrokymogram, the gallop sound was regularly fainter in those cycles in which the ventricular filling was small than in the alternating cycles in which the ventricular filling was greater (figure 1a). On other occasions, in the same patient, the degree of alternans was minimal, and the intensity of the gallop sound did not vary appreciably from beat to beat.

The Ballistocardiogram: The ballistocardiograms were very abnormal in all of the patients with gallop rhythm. Many of the ballistic complexes in a tracing were low in amplitude and bizarre in contour. In some records, interference due to respiratory movements was reduced by taking the ballistocardiogram with the patient in voluntary respiratory arrest following normal inspiration. In patients with protodiastolic gallop rhythm, the initial vibrations of the gallop (G in figure 5) began at or very shortly after the start of a downward motion of the ballistocardiograph (and of the body), which we interpreted as the result of the deceleration of the blood against the ventricular wall at the end of the stage of maximal ventricular filling. In individuals with presystolic gallop rhythm and a prolonged P–R interval, a similar downward motion was observed immediately after the

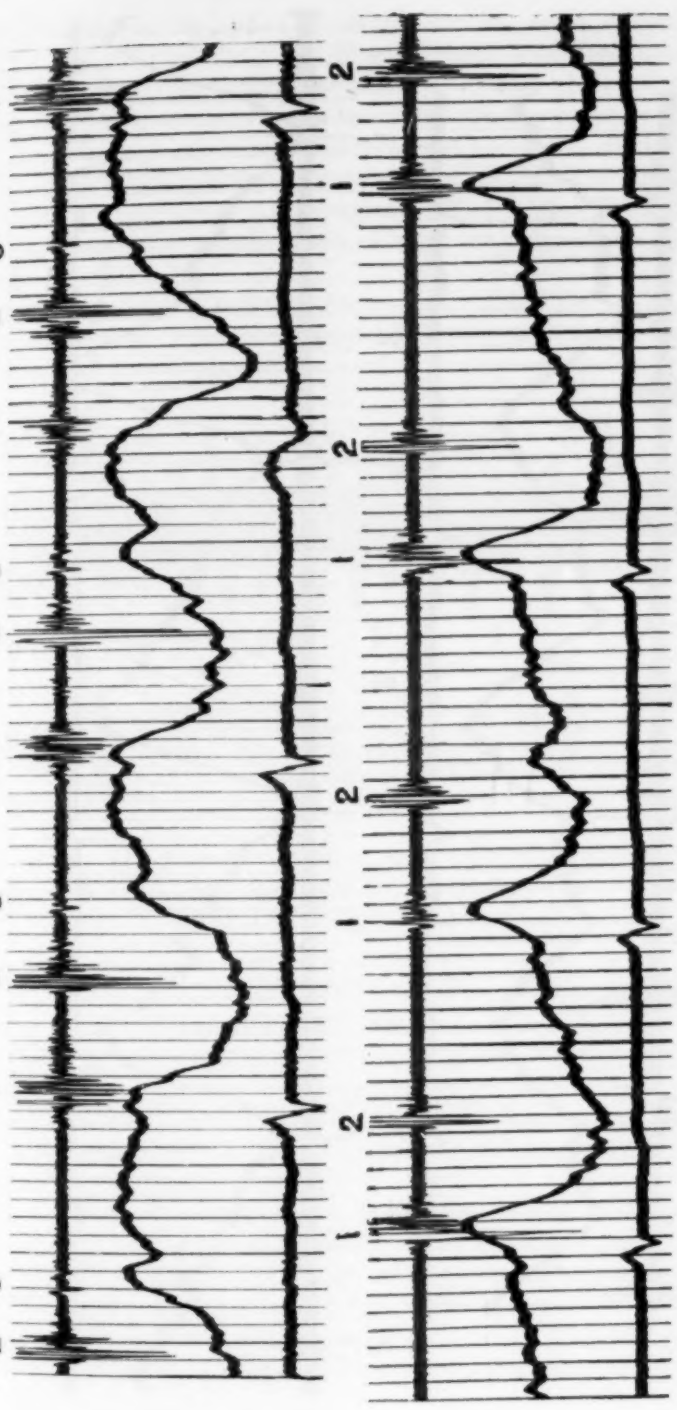

FIG. 3*a* (*above*). Protodiastolic gallop rhythm. Gallop sound 0.02 to 0.04 second before the toothlike peak of the early diastolic outward movement of the left ventricular border. Note "plateau curve." *b* (*below*). Same subject after digitalis. The gallop sound and the rapid early diastolic lateral motion have disappeared.

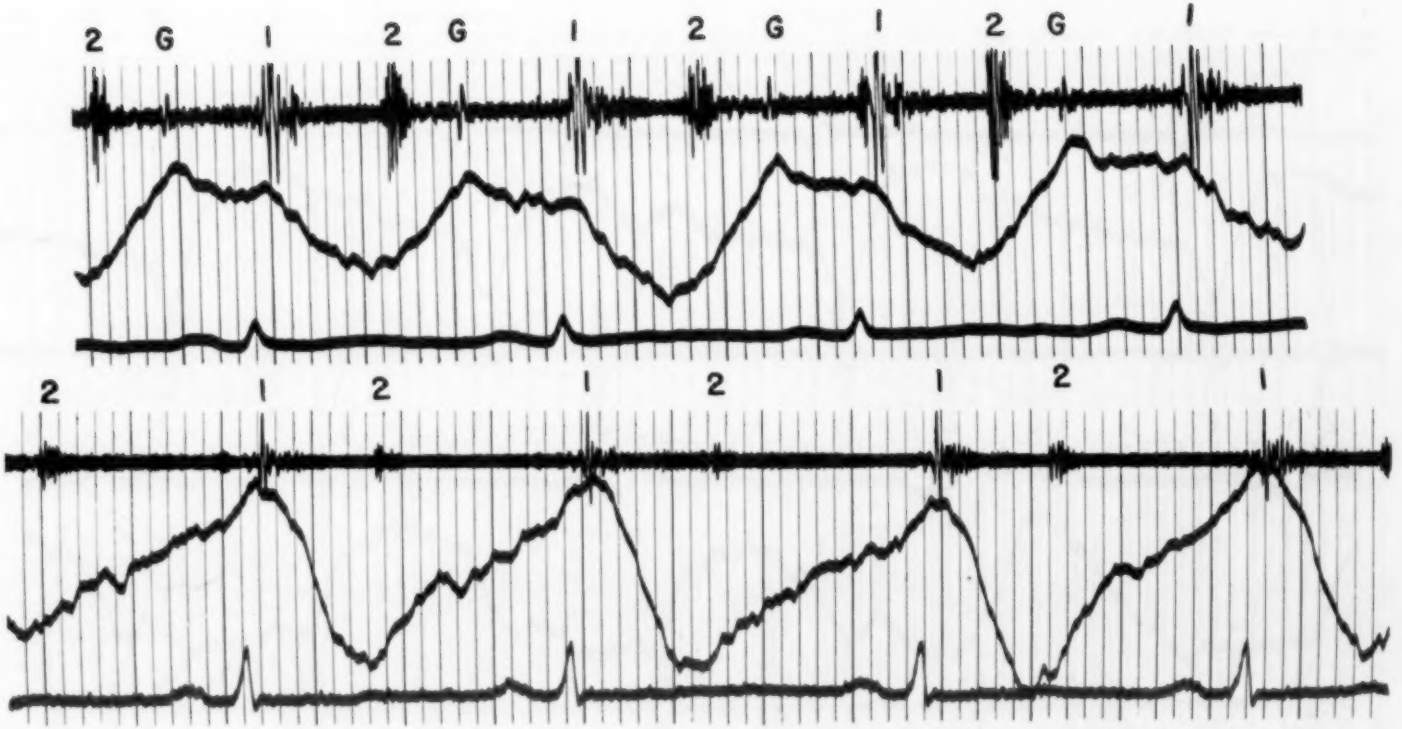

FIG. 4*a* (*above*). Protodiastolic gallop rhythm. Gallop sound immediately precedes peak of early diastolic outward movement of left ventricular border. Note "plateau curve." *b* (*below*). Same subject after digitalis. The gallop sound and the rapid early diastolic lateral motion have disappeared.

beginning of the gallop sound, evidently for the same dynamic reasons. When the P–R interval was short, it was difficult to differentiate this wave from those produced by ventricular activity. These observations are consistent and will be discussed further in a subsequent communication in which correlation has been made with intracardiac pressures, electrokymograph and sound recordings. This abnormal diastolic wave would usually become less prominent (but would not disappear entirely) after digitalis administration had resulted in improvement of the heart failure and disappearance of the gallop sounds.

Venous Pressure: Venous pressures taken from the antecubital veins were found to range from 158 mm. to 225 mm. of blood in these patients when abnormal movements of the cardiac border and gallop sounds were

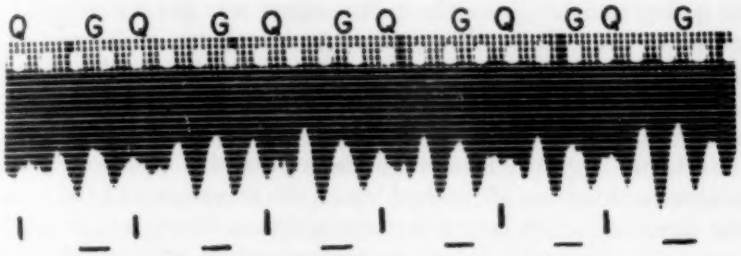

FIG. 5. Ballistocardiographic record of patient with protodiastolic gallop (*3a* above). Abnormal ballistic wave G in early diastole. The horizontal line, underlining the abnormal ballistic wave, should have been drawn to the right from the peak of the wave shown under G. Vertical line under Q indicates beginning of QRS complex of the simultaneously recorded electrocardiogram.

demonstrable. The pressure readings were lowered to levels between 110 mm. and 145 mm. of blood following the disappearance of the gallop sound and improvement of the electrokymographic curve.

DISCUSSION

Abnormal movements of the left ventricular border were demonstrated in all of the patients with gallop rhythm. During the periods when the gallop rhythm was present, certain characteristic electrokymographic patterns were observed. Different patterns also having characteristic features were observed in the same individuals when the gallop sounds had been made to disappear.

In the case of presystolic gallop, there was a rapid filling wave beginning 0.10 to 0.12 second after the onset of the P wave in the electrocardiogram, and reaching a peak just before the initial vibrations of the first heart sound. The gallop sound was observed to fall in the midst of this sharply rising portion of the curve, which was about 0.04 to 0.06 second before its peak (after allowing 0.015 second correction for the time lag of the electro-

kymograph). The fact that the gallop sound was shown to occur during the late stage but before the end of the rapid ventricular filling strongly suggests that the gallop sound is caused by the impact on the musculature of the ventricular wall of an inrushing column of blood. Since there is no reason to believe that the auriculoventricular valves could close during the inflow of blood, the participation of these valves in the production of the presystolic gallop sound appears to be excluded.

The finding of a shift of the gallop sound in cases of protodiastolic gallop rhythm to the earlier phases of diastole, corresponding to a similar shift of the ventricular filling wave, and the demonstration of an abnormal toothlike lateral expansion of the ventricular wall 0.01 to 0.04 second after the occurrence of the gallop sound, were evidences in favor of the thesis that a sudden impact and stretching of the ventricular wall cause the protodiastolic gallop sound. Since the gallop sound was always recorded before the peak of the ventricular filling curve and was never observed to occur after the peak of this wave, one must again conclude that the auriculoventricular valves do not participate in the production of protodiastolic gallop sounds.

It has been suggested that when the ventricular chambers are dilated with an abnormal volume of residual blood, the movements of the valves may be in the direction which favors the production of the gallop sound.[21] Our experience with one case of gallop rhythm and pulsus alternans was definitely not in accord with such a contention. In this case, the gallop sounds were definitely fainter when ventricular filling was diminished, owing to the presence of residual blood in the ventricular cavity, than in the alternate cycles where the filling was more complete. The time of the occurrence of the gallop sound with reference to the heart cycle recorded in the electrokymogram remained constant. This indicates that the gallop sound is more closely related to the magnitude of the wave of ventricular filling than to the position of the valves at the onset of the maximal ventricular filling.

A considerable elevation of venous pressure was consistently observed during those periods in which rapid early ventricular filling and its associated gallop sound were present. When venous pressure was normal or near normal, neither of the latter was observed. It is apparent that there is a causal relation between elevation of venous pressure and the associated phenomena of early, rapid ventricular filling and a protodiastolic gallop sound. The relation of venous pressure to presystolic gallop is more difficult to interpret. Three possible explanations are offered: (1) The force and volume of auricular emptying are augmented under the head of a high venous pressure. (2) Passive ventricular resistance to filling is diminished during periods when digitalis is withdrawn. (3) The slight increase in heart rate which regularly accompanied digitalis withdrawal moves auricular systole closer to the time of maximal passive auricular emptying. This approximation in time of the passive and active components of auricular

emptying is commonly recognized to result in "summation gallop."[4] Regardless of the true explanation of the observation, the fact remains that the presence and absence of the gallop sounds correlate with the appearance and disappearance of the presystolic wave of rapid filling.

The information obtained from the ballistocardiographic study was of considerable value to our study, although not entirely conclusive. The demonstration of abnormal ballistic waves in diastole in cases of gallop rhythm correlated well with the assumption that there was a sudden deceleration of the blood against the ventricular wall. With a normal or short P-R interval, however, this wave may be obscured by the systolic ballistic complexes.

The dramatic and consistent shift of the peak of the outward movement of the ventricular wall, following digitalis administration, from the late phases of diastole to the time when the first heart sound occurs in the subsequent cardiac cycle is of unusual interest to us. A rapid inward motion of the ventricular wall, simulating ejection, was observed to precede the first sound only in patients with gallop rhythm who were not receiving digitalis. Obviously, this could not have been a true representation of reduction of ventricular volume, since systole had not yet occurred. Likewise, an inward movement of the wall during the midportion of diastole in some patients with protodiastolic gallop could not have represented reduction in ventricular volume. It has been well recognized that movements of the left ventricular border of the electrokymogram result from alterations of the shape and rotation of the heart chambers in addition to alterations of the volume. It would appear that in the compensated patient movements of the border more closely approximate those of normal individuals and reasonably approximate changes of volume, whereas in those who are in congestive failure the shape and rotational movements are relatively large. Whether this may be the result of a direct effect of digitalis upon "myocardial tone" or be due to some other cause remains to be established. The change in time of the peak of outward left ventricular movement with digitalis administration was not accompanied by a change in the time of either the beginning or the peak of ejection, as measured by aortic knob recordings, with relation to electrical systole.

Likewise, we cannot assume that the outward movements of the left ventricle which we have correlated with gallop sounds are true representations of changes of ventricular volume. Nevertheless, in the absence of active myocardial contraction, it is reasonable to believe that any rapid outward motion must be directly the result of movement of blood into the ventricular chambers, even if the recorded effect is partly due to a change in volume and partly to a rotational change in shape. It has been believed that "densograms," obtained by placing the receptive slot of the phototube directly over the center of the heart, result in records which more closely approximate volume curves than records made from the left cardiac border.[22] In

the individuals studied here, it was found to be wholly impossible to obtain significant records by the "densogram" technic. The magnitude of the change of the anteroposterior diameter of the hearts was so small that the signal to noise ratio was intolerable.

SUMMARY

1. Electrokymographic, phonocardiographic, ballistocardiographic and venous pressure studies were made on 28 patients with hypertension and heart failure with gallop rhythm. During the course of the study, it was found necessary to select from this group a few individuals for detailed studies.

2. Two patients each with presystolic and protodiastolic gallop rhythms were selected. Gallop sounds disappeared and reappeared as digitalis was sequentially administered and withdrawn in each patient three or more times. Studies made during the period of digitalis administration were compared with those made after the drug had been withdrawn. The study indicates that a wave of rapid ventricular filling was indispensable for the production of either the protodiastolic or presystolic gallop sound, and that the sound occurs during this wave and not after its completion.

3. These observations support the view that an impact or sudden stretching of the ventricular wall is the chief cause of production of the gallop sound.

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FURTHER OBSERVATIONS ON THE USE OF LIBERALIZED DIETS IN THE TREATMENT OF DIABETES*

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THE treatment of diabetes can be made either a very difficult and disheartening problem to the patient, or a relatively easy one. It can be made an expensive problem, or relatively inexpensive. It can cause the patient considerable loss of time from his work, or very little, or none. All these are important factors, to be considered by the patient and the physician alike.

WHAT IS THE MEDICAL PROBLEM INVOLVED?

The medical problem involved in the control of diabetes is the control of abnormal hyperglycemia, for thereby the diabetes is controlled. When we have succeeded in the control of abnormal hyperglycemia we have reached our goal. No one can accomplish more than that. (I am not speaking of other medical conditions involved here.) To give more insulin in such a

TABLE I

Parallel Studies of Glycosuria and Glycemia

Age, Yrs.	Insulin Units	PZI Units	Blood Sugar			Urine Sugar		
			8	11	4	8	11	4
23	6	60	136	68	111	+	++	+
12	30	30	104	132	27	0	++	−
13.5	28	26	184	122	118	+	++	+
6	15	15	108	72	40	+	++	+
49	10	30	74	126	92	0	++	tr
27	14	30	104	106	126	ft	tr	+

++ is brick red. + is yellow. tr is green.

case, in an attempt to eliminate glycosuria if it be present with normoglycemia (and it often is), means producing hypoglycemia, which is misery for the patient, or bringing on insulin reaction, both highly undesirable. Dependence on urine examinations for control of the diabetic is NOT the ideal follow-up whether the patient be on insulin or just on diet, as such examinations are frequently misleading. Table 1 shows a few of the figures of parallel blood sugar and urine sugar estimations and the insulin dosage at the time. One can readily see how badly one would err were he to juggle the insulin dosage according to the urinary findings. But this is still being taught!

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 11, 1951.

Simplicity of Routine

Simplicity in working out a problem is essential. There should also be no loss of time in the procedure, either for the doctor or for the patient. The more complicated the routine procedure, the less effective; this applies especially to the instructions to the patient. Start by telling him a few essentials; on each subsequent visit add a bit. Thus he will have time to digest it. If you tell him too much at first, he will remember nothing.

Insulin and Diet

Up to the discovery of insulin in 1921, diet was the only thing used in the treatment of diabetes. In severe cases it had to be reduced to such low subsistence levels that severe diabetics became emaciated, discouraged skeletons, pitiful to behold. Yet this was the only way they could be kept alive, and most of them wanted to live.

With the advent of insulin, diets gradually became more liberal; in fact, in some instances they became too liberal—up to 6,000 calories a day. We know now that this was a mistake. Such diets usually required heroic doses of insulin, which was abnormal.

We were all steeped in the idea of fixed diets, weighed often to the second decimal point; and having been brought up on it, we continued to follow it even when insulin was used. On the whole, though, there was a certain amount of liberalization in the number of calories. The patients were taught to plan their meals—so many grams of carbohydrate, protein and fat—and to weigh their diets closely. This idea still persists to some extent, and is considered to be rational and scientific.

But on closer examination, and after years of observation, one comes to a different conclusion. Take a patient who is on a diet of, say, 2,200 calories: 200 gm. carbohydrate, 100 gm. protein, 111 gm. fat. What does such a diet represent? It is in fact a normal diet, such as you and I eat. Thus comes the question, Do these patients, three times a day, year in and year out, have to go through this rigmarole of planning and weighing their diets? Must they set themselves apart from the family at the dinner table, considering themselves as "different" from the family and thinking all the time of the things they "cannot have or do not have"? Do you realize what a psychologic problem this creates for them? Furthermore, relatively few continue to do this over any period of time. Thus the whole elaborate system breaks down. They either eat as they wish, within reason, or, if watched too closely by the family, who consider the diet the "sine qua non," they get extra food by stealth. This is bad, for it frequently means that they are getting sweets, such as candy or cake. And, to complicate things more, many (not all) when they are checked up show a good control, which makes them feel sure of themselves.

Something seemed wrong in our reasoning and our procedure. Apparently not all diabetics needed such a closely supervised and rigid routine.

Thus we had two categories of patients, and I felt it was necessary to differentiate between them. For those who were well controlled on a slightly restricted diet, a normal diet, there seemed no indication to subject them to a rigid routine. Even with such a routine they could not accomplish more; why make their lives miserable?

With this in mind, I began to experiment following World War II, when it was extremely difficult to get patients into hospitals. On a patient's first day at my office, his blood and urine sugar were checked three times before meals. The blood sugar was invariably high throughout the day, higher in some patients, lower in others. After the pre-supper checkup, I would start him immediately on PZI insulin, 20 to 30 units the first day. Following this, he came each subsequent morning before breakfast. The fasting blood sugar was taken to see how much of a drop there was from the day before. This is a direct index which tells whether to increase, keep the same, or decrease the dosage of PZI. When the fasting blood sugar reached normal on PZI I knew the dosage was adequate; to give more would have meant an insulin reaction the next morning. Each morning I instructed the patient how to measure and administer the insulin. After I had shown him on two successive mornings, he would give it himself under my supervision, so that any error could be explained and corrected. By the time the fasting blood sugar reached normal, the patient had learned to use the insulin correctly and from that time on was on his own.

When the fasting blood sugar reached a normal level, we knew that that particular dosage of PZI was correct. What we did not know was whether this particular dosage protected him not only in the morning but also throughout the day; i.e., whether the noon and the evening blood sugars too were normal or near normal. For some the PZI did the job. In others, where the noon or the evening or both blood sugars were elevated, a few units of the regular insulin had to be added to the PZI to control the postprandial hyperglycemia. When the dosage of the regular insulin, together with the PZI, was properly adjusted as found by subsequent checks, that was all there was to the problem, for thus we had returned the patient to his normal, physiologic status of normoglycemia throughout the day. The burden of proof, that prolonged hyperglycemia does not harm the patient, rests on those advocating this erroneous teaching. We need say no more about this controversial subject. Normoglycemia is physiologic. Hyperglycemia is not!

When we try to evaluate the blood sugar findings we have to consider this: It is not the height of any individual blood sugar which gives us the specific answer. The important thing is, How many hours out of the 24 does that patient, whatever his routine, carry an elevated blood sugar, and how many hours of the 24 is the blood sugar normal? Even a normal person carries some elevation of the blood sugar each day, the so-called postprandial hyperglycemia which is physiologic and of but short duration—an

hour, an hour and a half or at most two hours after each meal. Thus, if we take the last figure and multiply it by three (three meals a day), we see that a normal person can carry elevated blood sugar up to six hours a day, or 25 per cent of each 24 hours. This, then, we take as our criterion for the evaluation of a diabetic control. If such a diabetic, whatever his routine, carries hyperglycemia 25 to 30 per cent each day, this is normal and we can accept it as a good control. If the hyperglycemia lasts 50 per cent of the day, readjustment of dosage of insulin is indicated. If the hyperglycemia is 100 per cent of the day, this is bad and calls for prompt handling. In all cases here presented you will note that on the first examination patients carried hyperglycemia 100 per cent of the time, thus the indication for the immediate use of insulin. The practical reason for taking the three blood sugars a day, one before each meal, is to see if the blood stream has cleared itself of the excess of sugar before the next meal, which is about three hours. If so, then the response is perfect, for it is physiologic, or normal, as in a nondiabetic, whose blood stream always clears itself of excess sugar before the next meal.

Now about the diet. I have already mentioned that our present diets of 2,000 to 2,500 calories are, for all practical purposes, normal diets. Thus, if a patient eliminates from his diet sugar, pastry and soft drinks, and restricts his bread to two slices or less with each meal (if he has a helping of potatoes he does not eat bread); and uses fresh fruit, or cheese and crackers for dessert, or fruit canned without sugar, he can eat whatever is served to the rest of the family. He is warned to eat with moderation and to watch his weight. If he is gaining in weight it means that he is taking in too many calories and must cut down on his eating. Once a week, a helping of ordinary ice cream without sauce helps to satisfy the craving for sweets. Also, he does not feel set apart from the rest of the family.

Such a dietary routine is simple. The patient no longer feels that he is "different" from the rest. He eats what they do, but learns to use moderation. He does not have to think constantly of all the things he cannot have. Thinking of them creates a tremendous craving for these very things, which sooner or later leads him to step over the restrictions of a liberalized diet. The psychologic aspect of this is so very important that we cannot afford to disregard it.

Now comes the question, Has it worked? If it has then I feel sure the procedure and the reasoning were correct; if not, I would have had to go back to the old routine of planning and weighing or estimating the various portions of the diet.

I began the new procedure in 1946, when I returned from service. I soon found that it was working—in fact, working beyond my expectations. And, most important, such a procedure made the life of a diabetic a much happier one than it had been on the old, complicated routine. Thus I felt enthusiastic about the results, and in 1948 I published the preliminary report

of my work, which was gratifying to me. Now, three years later, I am presenting further observations on the use of liberalized diets, which are merely a confirmation of the original observations except that they now extend over a longer period of time. There have been very few failures. Indeed, these were but part failures, and easily corrected. Over 90 per cent have had successful results, a good batting average. Now to show you in graphic charts some of the results on these patients:

Case Reports

Case 1, chart 1A. Male, 27 years of age. Diabetes had been discovered three months before, at which time the fasting blood sugar was 280 mg. per cent. His father was a diabetic; otherwise the history was negative. At the beginning, while the blood sugar was 280, his physician put him on a diet, and three weeks later the fasting blood sugar was 170 mg. per cent. I first saw him on October 4, 1949, at which time the three blood sugars, three times a day, before meals, were 171, 210 and 134 mg. per cent, and the urine sugar was zero, trace, trace. Largely because of his age, I started him immediately on 20 units of PZI. On this the fasting blood sugar promptly dropped to normal, and after five days of office procedure he was on his own, taking 20 units of PZI each morning. He has shown a reasonably good control for a year and seven months.

Case 2, chart 1B. A 65 year old man came to my office with the classic symptoms of diabetes of three months' standing. His mother had died of diabetes; otherwise the history was negative. When I first saw him, on November 2, 1948, his blood sugars were 162, 150 and 272 mg. per cent, and the urine sugar was +, ++, +. I started him immediately on 20 units of PZI, on which the fasting blood sugar promptly came down to normal. After five days all PZI was discontinued, and subsequent checks showed a normal blood level throughout the day. This is what one would expect in a man of 65; he should get along without insulin and on a slightly restricted diet. Then the patient began to lose weight, became irritable and finally felt quite run down. After 17 months without a checkup he came to see me. The blood sugars were all high. Insulin was reinstituted, 10 units of insulin and 20 units of PZI the first day, and after that 20 units of NPH insulin. After checkup in the office on four subsequent days he continued on this dosage. Now, three months later, he shows good control on 16 units of NPH. Here we see one interesting thing: It is often said that patients as old as this man can manage without insulin. We tried it and it worked for over a year, but then he broke down again and was worse off physically than at the beginning, having gone down in weight from 150 to 122 pounds. This shows that one cannot make any generalizations about using or not using insulin because of old age. The important thing is to have a proper checkup to be sure that insulin is not needed. This man is certainly in a different physical condition on insulin and is only too happy to use it, as it gives him health and energy.

Case 3, chart 1C. A 33 year old man came to my office stating that glycosuria had been discovered a week before and that for two months he had had nocturia and dryness of mouth. His father was a diabetic. The patient had had "flu" two weeks before; the history was otherwise negative except that he was 35 per cent overweight and had been as much as 50 per cent overweight. On his checkup the blood sugars were 263, 362 and 282 mg. per cent, and the urine sugar was ++, ++, ++. I started him immediately that same evening on 10 units of insulin and 25 units of PZI, the following day on 20, and after that on 25 units PZI daily. After five days at the office the fasting blood sugar came close to normal and he went on his own. Subsequent checks show a good control to date, now almost two years. An obese patient

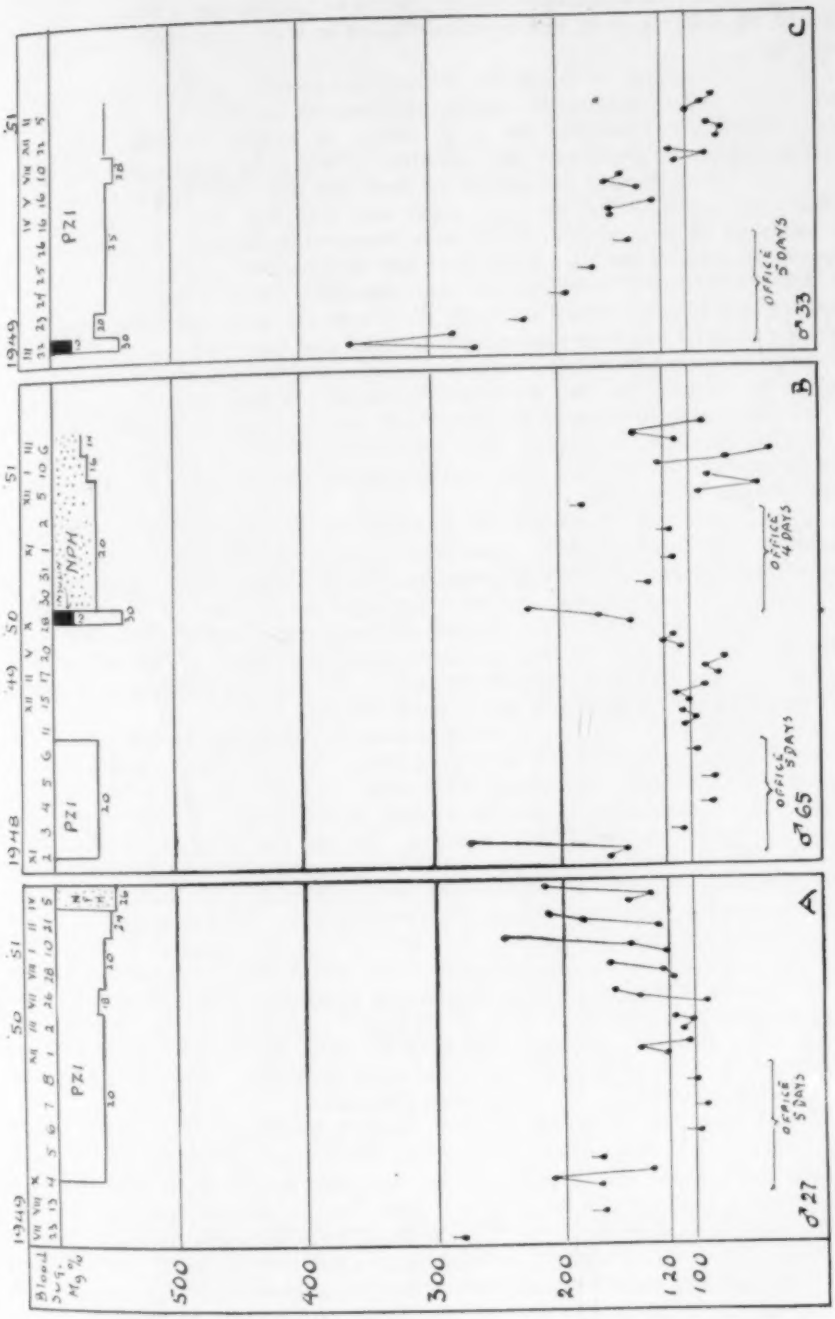
Blood Sug. Mg %
500
400
300
200
120
100
1949
1948
50
51
PZI
NPH
OFFICE 5 DAYS
OFFICE 4 DAYS
σ'27
σ'65
σ'33
A
B
C

CHART 1.

like this no doubt could be controlled on a rigid diet alone, in an attempt to reduce the weight, but such a procedure would have to be carried out in a hospital, as rigid diets of 800 calories or so just do not work out at home, especially if the patient is working.

Case 4, chart 2A. A 55 year old business man came to my office because of glycosuria which had been found on routine examination two days before. He had had thirst, polyuria and nocturia for three weeks. A brother and sister had died of diabetes; otherwise the history was negative. The fasting blood sugar was 236 mg. per cent. When checked throughout the next day the blood sugars were 227, 285 and 272 mg. per cent and the urine sugar was ++, ++, ++. I started him immediately on 20 units of PZI, which were increased to 30 units. The fasting blood sugar came down to normal. After seven days at the office he was on his own, taking 30 units of PZI each morning, and the subsequent checks were all normal. The dosage was gradually reduced to 25, 20, 18, 10 and five units, and after being on PZI for 16 months, it has been discontinued to date, now over two years. I think it is important to carry patients on insulin for a period long enough to give the pancreas a chance for recovery, so that when they discontinue it there is a reasonable chance of their not having to resume. Further, these patients should be checked periodically, to be sure they are controlled. This man is careful of his slightly reduced diet. The fact that his brother and sister had died of diabetes, serves as a deterrent to his being careless in his habits.

Case 5, chart 2B. A 63 year old man came to my office with the complaint that glycosuria had been found three weeks before, and wanted to know if he had diabetes. His personal history was otherwise negative. On first checkup his blood sugars were 306, 275 and 252 mg. per cent, and the urine sugar was +, ++, ++. I started him immediately on 20 units of PZI; the fasting blood sugar kept dropping on 25 units daily, so after 11 days he was on his own on 25 units of PZI. His subsequent checks were good. The PZI was gradually reduced to 15 units, on which he has remained well controlled over a period of nearly three years.

Case 6, chart 3A. A 53 year old man came in stating that he had shown glycosuria and hyperglycemia off and on for six years. He had been on a diet, but a few days before I saw him his fasting blood sugar was 280 mg. per cent, which had scared him. There was no history of diabetes in the family. He was slightly overweight; otherwise the history was negative. On the first checkup his blood sugars were 214, 250 and 162 mg. per cent, and the urine sugar was +, ++, ++. That same evening I gave him 20 units of PZI, but he wanted to try diet alone for three weeks, to which I consented. When I checked him three weeks later the blood sugars were a bit higher than the first time, and he saw that on diet alone he could not be controlled and that insulin was indicated. As I was going out of town, I had only two days in the office in which to teach him how to administer the insulin. The blood sugar dropped promptly on 20 units of PZI, and subsequent checks showed a good control. The PZI was gradually reduced to 10 units, and on January 26, 1951, two years from the start of insulin, I discontinued it altogether. His subsequent check, a month later, showed a perfect control on diet alone.

Case 7 chart 3B. A 52 year old man came to the office with the complaint that glycosuria had been found a few days before. He had had thirst, frequency of urination and nocturia for over a year, and had lost eight pounds in weight. He had a brother and a sister who were diabetic; otherwise, the history was negative. The blood sugars on the first day were 197, 300 and 256 mg. per cent, and the urine sugar was trace, ++, ++. I started him immediately on 10 units of insulin and 20 units of PZI, and each subsequent morning he received 20 units of PZI. The fasting blood sugar came to normal quickly, so that after seven days he was on his own. He did well and showed a perfect control. After a little over a year all insulin was discontinued, and he shows a perfect control on diet alone.

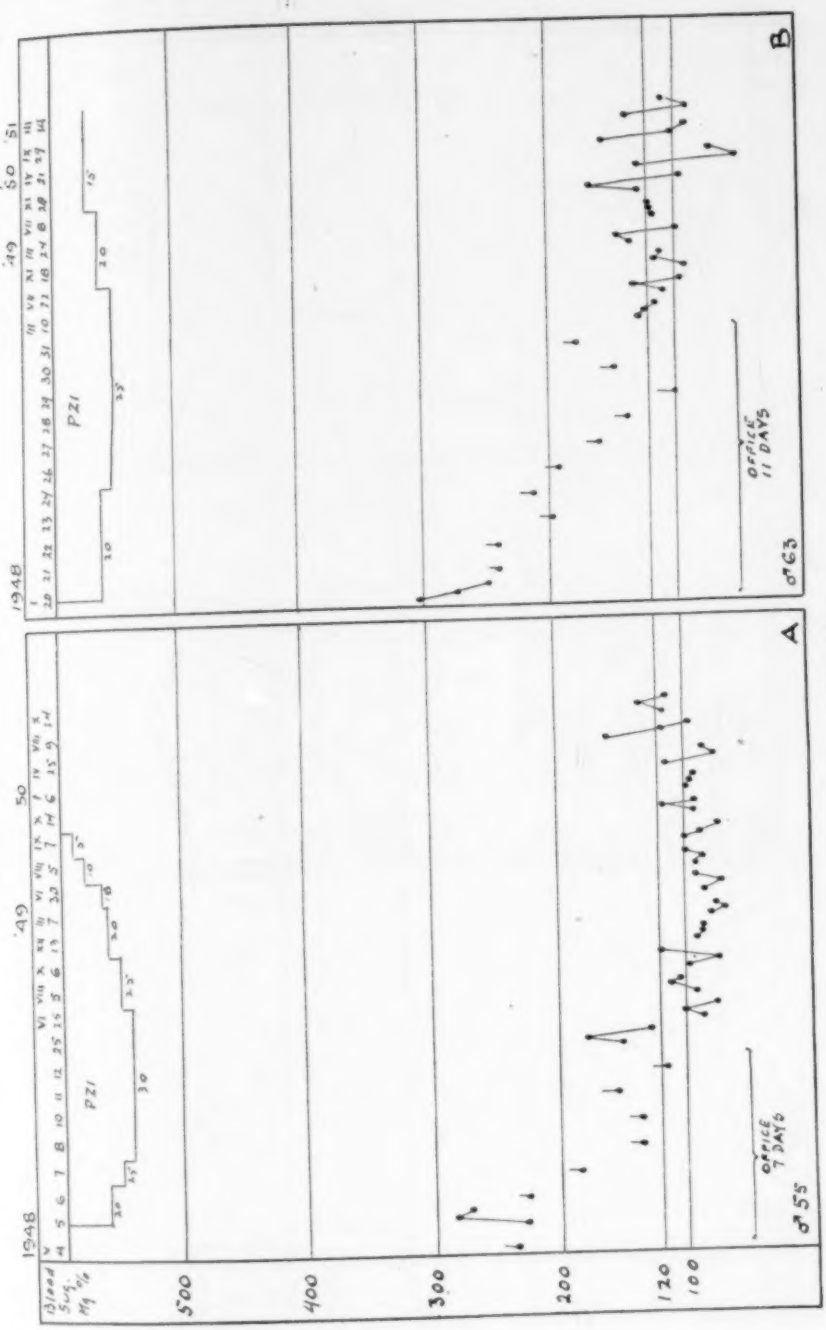
Blood Sugar Mg %
500
400
300
200
120
100
1948
'49
'50
PZI
OFFICE 7 DAYS
OFFICE 11 DAYS
A
B

CHART 2.

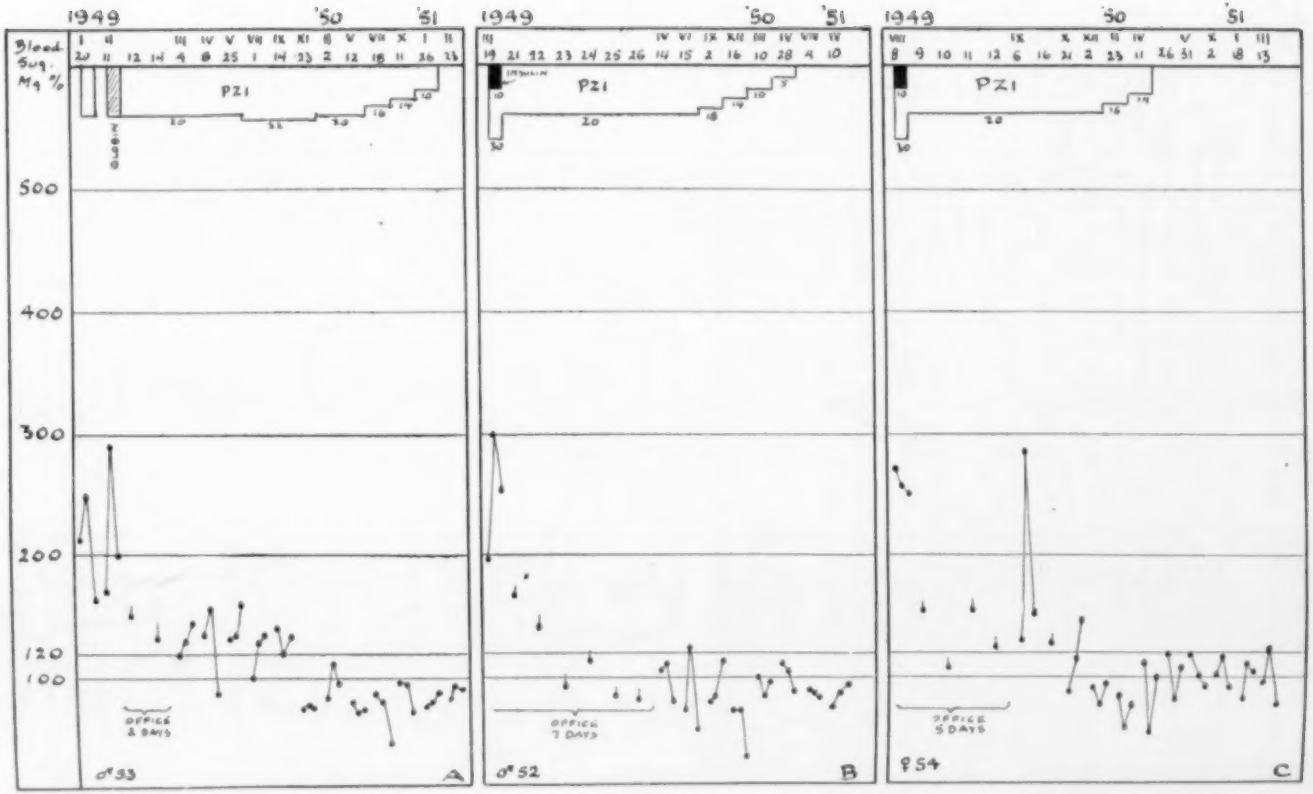
1949
'50
'51
Blood Sug. Mg %
500
400
300
200
120
100
PZI
OFFICE 2 DAYS
♂ 33
A
OFFICE 7 DAYS
♂ 52
B
OFFICE 5 DAYS
♀ 54
C

CHART 3.

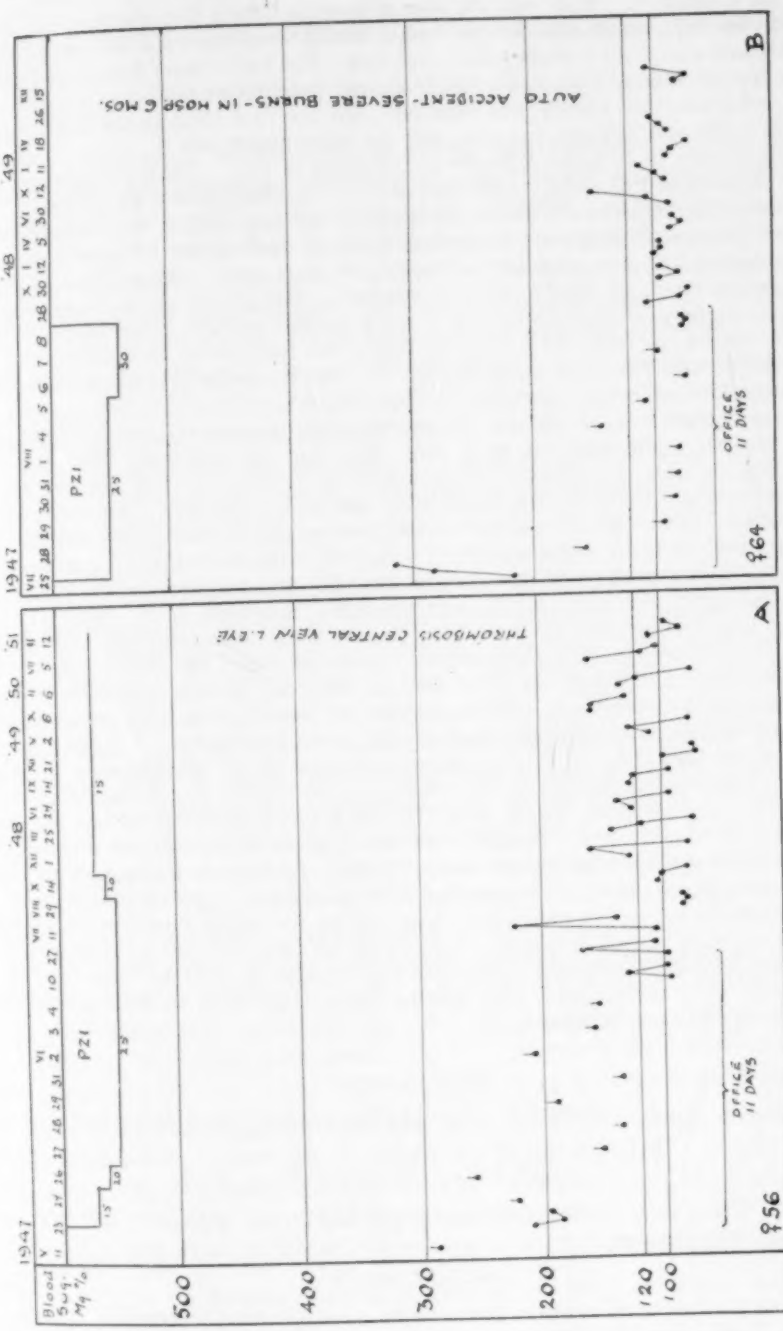
A
B
THROMBOSIS CENTRAL VEIN L. EYE
AUTO ACCIDENT- SEVERE BURNS- IN HOSP 6 MOS.
PZI
OFFICE 11 DAYS
956
964
Blood Sugar Mg %
500
400
300
200
120
100
1947
48
49
50
51

CHART 4.

Case 8, chart 3C. A 54 year old woman came in stating that glycosuria had been found a few days before and that she had a fasting blood sugar of 320 mg. per cent. She felt well except for a slight pain in her legs. She had a heavy history of diabetes in the family: father, mother, brother, maternal grandfather and several uncles and aunts; otherwise her history was negative. On the first checkup the blood sugars were 272, 258 and 250 mg. per cent, and the urine sugar was +, +, +. I started her immediately on 10 units of insulin and 20 units of PZI. The next morning I put her on 20 units of PZI daily. After five days at the office she was on her own. The first check after that showed definite elevation of the blood sugar, but I had her continue on the same dosage, and all subsequent checks were normal throughout the day. The dosage of PZI was gradually reduced to 14 units a day, and on April 11, 1950, nine months later, all insulin was discontinued. Subsequent checks were normal. The question here is, Will she be able to carry on on diet alone in the future? Only periodic checks will tell. She certainly has a bad background of diabetes. She is very sensible about her diet, however; she has seen too much of diabetes and wishes to manage without insulin if possible. Time will tell.

Case 9, chart 4A. A 56 year old woman came in because glycosuria had been found recently. She was put on a diet. She had no symptoms. Her maternal cousin had diabetes; her history was otherwise negative except that she was 24 per cent overweight and had been as much as 36 per cent overweight. She had a slight hypertension. On original examination the blood sugars were 210, 184 and 197 mg. per cent, and the urine sugar was ++, ++, ++. The fasting blood sugar, which had been taken elsewhere 12 days before, was 289 mg. per cent. I started her on PZI immediately, 15 units, which was gradually increased to 25 units. On the eleventh day, her last day, all three blood sugars were normal and she went on her own. The PZI was gradually reduced, to 15 units to date. Her rechecks have been fairly satisfactory, although she is of the type who just cannot or will not stick to any reduction in diet. She is still overweight, but on the whole has shown a reasonably good control of her diabetic condition for about four years.

Case 10, chart 4B. A 64 year old woman came to my office because of glycosuria. There was no diabetes in the family, and her history was otherwise negative. On the first day her blood sugars were 217, 282 and 316 mg. per cent, and the urine sugar was ++, ++, ++. I started her immediately on 25 units of PZI and the blood sugars came down promptly. After 11 days of follow-up she was on her own. As the three blood sugars of the last day were all normal, I discontinued all insulin. Subsequent checks, on diet alone, have been normal for nearly three years. In 1949 she was severely burned in a serious automobile accident and had to be hospitalized in another state for six months. Not even that experience upset her diabetes. Here we have an older woman who, after getting the original boost by insulin, is able to carry on on diet alone without insulin.

Conclusion

Diabetes can be controlled, and well controlled, on liberalized diets, as I have shown. A follow-up of the patient is necessary. Such a diet eliminates the feeling of "sacrifice" and the great psychologic stress that goes with it. This, in turn, means more happiness in the patient's life and thus more accomplishment.

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VARIABILITY OF SIGNS IN MULTIPLE SCLEROSIS *

By Irving C. Sherman, M.D., *Chicago, Illinois*

In a recent study of the effect of tetraethylammonium chloride on the course of multiple sclerosis, there became available for analysis a group of patients who were examined on repeated occasions. These patients frequently showed a variability in objective signs which at first was thought due to the treatment. However, careful study, as reported elsewhere,[1] revealed that actually the treatment had no effect on the course of the disease.

If a drug is efficacious in the treatment of multiple sclerosis, then the majority of the pathologic signs should show amelioration. Actually it was found that, although a certain number of such signs showed improvement, an equally significant number showed an increase in severity. Secondly, it was observed that improvement most frequently occurred in gait, strength, cerebellar signs, clonus and vibration perception, but similar numbers of other patients showed an increase of signs in these same five major categories. Thirdly, despite frequent administration of the drug over a long period, it was found that there was an increase in the percentage of signs improving, but at the same time there was also an increase in the percentage of signs showing progression, indicating that these changes are the influence of time and not of the treatment. Finally, three patients were observed who suffered acute episodes of neurologic disease while on treatment: one had two attacks of paraplegia, one had a transient monoplegia, and one had a severe cerebellar ataxia appearing abruptly in one arm. Therefore, it was concluded that the variability in the objective signs must be an intrinsic part of the disease process.

The material consisted of 42 patients with an unequivocal diagnosis of multiple sclerosis. Many of these had been previously diagnosed and treated at clinics in various parts of the country. All of them were observed for a period of three weeks in Michael Reese Hospital. Twenty-three patients were followed personally after discharge for from three to 30 months. There were six patients with persistent paraplegia. Thirteen were so disabled as to be able to walk only with great help and then only to a limited degree. The remaining 23 were sufficiently ambulatory to keep up with their work or take care of their household obligations fairly well.

Method of Analysis

In order to analyze objectively the progress of each case, certain constant, easily followed criteria of the neurologic status were chosen for specific study.

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Eighteen items were selected, and each was graded in accordance with the severity of the disturbance at the time of examination. Because of the possible wide variations, gait and strength were graded in five degrees: normal was represented as 5, and increasing degrees of disability graded downward through 4, 3, 2 and 1. The remaining criteria were given only three grades, normal being represented as 3, moderate disturbance as 2 and marked disturbance as 1. The 16 criteria graded thus were tone, stance, cerebellar signs, tendon and periosteal reflexes, abdominal reflexes, clonus, Hoffmann's sign, Babinski's sign, position sense, vibratory sense, pain, light touch, nystagmus, optic discs, speech and bladder status. If minor changes were noted of insufficient degree to warrant a change in a full grade, these were recorded as plus or minus.

The recorded examinations for each patient were reviewed at one sitting, and each component was graded according to the above standards. Any change in a particular criterion became immediately evident by comparing the examinations on successive dates. This method, however crude, permitted the tabulation of a concise and realistic objective summary of each patient's course without the influences of the patient's subjective responses. This could then be charted as is shown in the following example:

M. L. D., white female, age 38, became ill three months before coming under observation. She had suffered numbness of the left thigh and perianal region for three months, unsteadiness of gait and dizziness associated with vomiting for two months.

The method of recording and analysis in this particular patient is illustrated in table 1.

TABLE I

Individual Patient Analysis Chart

Diagnostic Criteria	1949 July		1949 Aug.		1949 Sept.	1949 Oct.	1949 Nov.	1950 Jan.
	10	28	1	5	8	14	22	11
Gait	4+	4+	4+	4+	5	5	5	5
Strength	5	4	4+	4+	5	5	5	5
Tone	3	3	3	3	3	3	3	3
Stance	3	2	2	3	3	3	3	3
Cerebellar signs	2	2	2	2	2+	2+	2+	2+
Tendon reflexes	2	2	2	2	2	2	2	2
Abdominal reflexes	2	2	2	1	1	1	1	2
Clonus	3	3	3	3	3	3	3	3
Hoffmann's sign	3	3	3	3	2	1	3	3
Babinski's sign	3	3	3	3	3	3	3	3
Position sense	3	3	3	3	3	3	3	3
Vibration sense	3	3	3	3	3	3	3	3
Pin perception	3	3	3	3	3	3	3	3
Cotton perception	2	2	2	2	3	3	3	3
Nystagmus	1	1	1	1	1	2	3	2
Discs	3	3	3	3	3	3	3	3
Speech	3	3	3	3	3	3	3	3
Bladder	3	3	2	3	3	3	3	3

The numbers recorded for any one neurologic criterion, followed across the chart, show quickly what happened in that particular category. Thus, it is apparent that a mildly disturbed gait returned to normal. The strength was normal at the beginning and at the end of our observation period, but in the interim the patient developed a paresis of the right upper extremity from which she recovered quickly. Stance and bladder control were normal at first and became disturbed, but for only a short time. She had a mild intention tremor in both upper extremities which disappeared from one arm. The abdominal reflexes, which were easily exhausted at first, disappeared for a while and then returned feebly. Bilateral Hoffmann's signs appeared temporarily after two months. She had a decreased perception of cotton on one lower extremity, which returned to normal. There was a very obvious nystagmus which returned to normal after four months, only to reappear two months later. All other categories were normal.

Results

To avoid the problem of dealing with individual cases, it was considered feasible to study the sum total of all the pathologic signs in all patients. This would give a picture of the total pathologic disturbance in the patients and would permit drawing a base line from which improvement or progression could be measured. Each of the 18 criteria in the neurologic examination was analyzed in terms of frequency of occurrence, instances of improvement or progression, appearance of findings not present in the initial examination, and the number showing no change. Thus it could be determined what proportion of pathologic signs present at the beginning of treatment showed improvement. This could be compared to the total of those signs which were present and progressed, in addition to those which first appeared during the course of observation.

A. Analysis after Three Weeks of Observation in Hospital: In this group of 42 patients there were 466 pathologic findings at the onset (table 2). At the end of three weeks of observation a total of 69 signs showed improvement. These were scattered among a total of 32 cases, so that it is evident we are not dealing with a small group of patients with a remitting type of disease. In contrast to this, there were 21 instances of progression of signs, but at the same time 18 new instances of pathologic disturbance appeared, making a total of 39 signs of progression which were scattered among 20 patients. Of the 69 instances of improvement, 39 were accounted for by changes in five criteria, namely, gait, strength, cerebellar signs, clonus and vibratory sense. It is notable also that 17 of the 39 instances of progression and newly appearing findings occurred among the same five criteria. There was diminution of strength in five cases (eight improved); cerebellar signs became worse in three cases (nine improved); clonus became worse in six cases (seven improved). It is noteworthy that in the great bulk of the pathologic findings there was no change at all.

B. Analysis of Long Term Observation: This group consisted of 23 of the original 42 patients. Seven were observed for three months; six for three to 12 months; five for 12 to 18 months; four from 18 to 24 months, and one for 30 months.

In these patients the initial examination was compared with the last examination while under observation (table 3). There were 265 pathologic signs at the onset. There was no change in 160 instances. There was improvement in 66 signs scattered among 21 cases. In contrast to this, there were 39 instances of progression, and 19 in which signs appeared which had not been previously present, making an actual total of 58 instances of progression among 18 patients.

TABLE II

Three Weeks' Observation (42 Cases)

Criteria	Number showing Pathology	Number showing Improvement	Number showing Regression	Number showing New Findings	Number showing No Change
1. Gait	39	7	1	0	31
2. Strength	28	8	4	1	16
3. Tone	30	2	0	1	28
4. Stance	27	4	0	2	23
5. Cerebellar signs	33	9	2	1	22
6. Tendon reflexes	41	0	0	0	41
7. Abdominal reflexes	42	3	2	0	37
8. Clonus	34	7	4	2	23
9. Hoffmann's sign	21	3	4	3	14
10. Babinski's sign	37	3	1	1	33
11. Position sense	17	2	1	2	14
12. Vibration sense	17	8	1	1	8
13. Pin perception	3	1	0	0	2
14. Cotton perception	10	3	0	1	7
15. Nystagmus	30	4	1	1	25
16. Optic discs	15	0	0	0	15
17. Speech	8	0	0	1	8
18. Bladder status	34	5	0	1	29
Totals	466	69	21	18	376

In this long-term follow-up group, of the 66 instances of improvement, 29 were accounted for by five criteria, namely, gait, strength, cerebellar signs, clonus and vibratory sense. In these same criteria there was a total of 22 instances of progression. For example, there was improvement in gait in four cases (four were worse); strength improved in three cases (five were weaker); cerebellar signs improved in eight cases (progressed in seven); clonus improved in six cases (progressed in three), and vibration improved in eight cases (progressed in three).

It is apparent that there is a marked variability of certain objective signs in multiple sclerosis. Almost half of the total changes occurred in five criteria. The changes were in both directions, some patients improving and others becoming worse.

Since the above analysis compares only the first examination with the last examination while under observation, a more detailed study of this variability was pursued by studying the course of each patient. Each item of the neurologic examination was observed through the repeated examinations for any improvement or progression. Where the changes occurred in either direction more than once, this was ignored, so that the analysis reveals how many of the 23 patients improved or regressed in any one sign at least once. In three patients, acute episodes occurred: one had two attacks of paraplegia, one had a brief monoplegia, a third had the rather sudden appearance of severe intention tremor in one upper extremity.

TABLE III

Long Term Observation (23 Cases)

Criteria	Number showing Pathology	Number showing Improvement	Number showing Regression	Number showing New Findings	Number showing No Change
Gait	21	4	3	1	14
Strength	15	3	4	1	8
Tone	14	3	5	4	6
Stance	16	5	3	1	8
Cerebellar	19	8	4	3	7
Muscle stretch reflexes	22	1	1	0	20
Abdominals	23	3	1	0	19
Clonus	21	6	3	0	12
Hoffmann's	14	5	5	2	4
Babinski's	19	5	1	2	13
Position	9	3	1	0	5
Vibration	11	8	2	1	1
Pin	1	1	0	1	0
Cotton	7	2	1	1	4
Nystagmus	15	6	1	0	8
Discs	12	0	2	1	10
Speech	7	0	0	0	7
Bladder	19	3	2	1	14
Totals	265	66	39	19	160

In this group of patients (table 4) who had numerous repeated examinations, it was found that gait improved in six patients and regressed in eight. Strength improved in six and regressed in nine. Tone improved in four and regressed in eight. Stance improved in four and regressed in five. Cerebellar signs improved in 15 and increased in 12. Tendon and periosteal reflexes improved in two and regressed in one. Abdominal reflexes improved in six and regressed in five. Clonus improved in 11 and increased in six. Hoffmann's sign improved in 12 and increased in 10. Babinski's sign improved in seven and increased in five. Position sense improved in six and regressed in five. Vibration sense improved in nine and regressed in seven. Pain sense improved in one and regressed in one. Touch improved in seven and regressed in three. Nystagmus improved in 12 and increased in 12. Changes in the optic discs appeared to be improved in two

and worse in three, the two cases of improvement being doubtful. Speech improved in none and regressed in none. The bladder disturbances improved in 11 and increased in nine.

From this analysis it is apparent that all objective signs studied, except for speech and optic discs, improved or became worse at one time or another. In this series speech did not change, and in three patients the discs became worse but none improved significantly. The signs which show the greatest variability are cerebellar, clonus, Hoffmann's, nystagmus and bladder disorders. At least half of the patients showed changes in these categories. Vibration, position and cotton perception also fluctuated surprisingly often. The appearance and disappearance of an abdominal reflex or Babinski's sign are not uncommon.

TABLE IV

Analysis of Variability of Signs in 23 Patients with Multiple Sclerosis Who Had Numerous Examinations

Criteria	Improved	Regressed
Gait	6	8
Strength	6	9
Tone	4	8
Stance	4	5
Cerebellar	15	12
Tendon reflexes	2	1
Abdominal reflexes	6	5
Clonus	11	6
Hoffmann's sign	12	10
Babinski's sign	7	5
Position sense	6	5
Vibration sense	9	7
Pin perception	1	1
Cotton perception	7	3
Nystagmus	12	12
Discs	0	3
Speech	0	0
Bladder	11	9

One can only guess at the reasons for these fluctuations. Perhaps strength and gait may improve as a result of rest. Sensory signs may vary with the patient's attitude or the examiner's insistence upon coöperation. However, such findings as clonus, pathologic reflexes and nystagmus must be dependent upon some variability in performance of function in the damaged but not destroyed components of the nervous system.

SUMMARY AND CONCLUSIONS

A critical method of objective evaluation of the fluctuation of signs in multiple sclerosis is presented.

A group of 42 patients was observed in hospital for three weeks and the clinical status at discharge was compared with that on admission. Out of 466 pathologic findings, there were 69 instances of improvement scattered among 32 patients and at the same time 39 signs of regression among 30 patients. Twenty-three patients were observed for from three to 30 months.

Comparison of the initial and final examinations revealed that, out of 265 pathologic signs, there were 66 instances of improvement scattered among 21 patients and 58 signs of regression in 19 patients.

A more detailed analysis of the signs which varied in frequency or intensity was permitted by a study of the repeated examinations during the course of the illness in those patients observed for from three to 30 months. The most variable signs were cerebellar, clonus, Hoffmann's nystagmus and bladder disorders. All other signs fluctuated at one time or another except for speech. There also appeared several instances of the acute episodic neurologic disorder so familiar in multiple sclerosis.

This study reiterates what has been accepted as one of the diagnostic criteria for multiple sclerosis, namely, its episodic and recurrent nature in some cases. Furthermore, it calls attention to the fact that there may be variability in the objective signs without the appearance of any gross episodic disorders.

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MYOCARDIAL INVOLVEMENT IN ACUTE NONSPECIFIC PERICARDITIS: A REPORT OF THREE CASES *

By JOHN GODFREY, M.D., *Olean, New York*

FOR the past 10 years, increasing interest has been shown in acute pericarditis of obscure etiology, known commonly as acute nonspecific pericarditis or acute benign pericarditis. This syndrome is characterized by its onset with substernal or anterior thoracic pain, sometimes severe enough to require differentiation from myocardial infarction,[1, 2] and is associated with a pericardial friction rub, fever, leukocytosis and elevated sedimentation rate in the majority of instances. A pericardial effusion has appeared in approximately 20 per cent of these cases, and pleural effusion in about 25 per cent. Complete recovery in two to 12 weeks has been the rule, although relapses have been noted. The clinical picture has been well documented.[1-10] The frequent association with upper respiratory infections has been noted.[9, 11-13] The diagnosis continues to be one of exclusion, however, since no etiologic agent or specific diagnostic test has been reported.

The benign nature of this syndrome has been stressed in most reports [4, 8, 9] and, with few exceptions, little attention has been paid to the possibility of significant myocardial involvement. Wolff [14] reported five cases showing cardiac enlargement, which disappeared within one month in each instance. He thought this analogous to the cardiac dilatation appearing in acute infections, or perhaps due to involvement of the subepicardial myocardium. Transient cardiac dilatation in the course of acute nonspecific pericarditis has also been commented upon by Barnes and Burchell [2] and Burchell.[3] However, Tabenhaus and Brams,[15] in reporting the use of aureomycin in this condition, state that "pericardial effusion may develop and may require paracentesis but no permanent damage or harmful sequela has been reported."

It is the purpose of this communication to report three cases, all typical of acute nonspecific pericarditis, which showed evidence of myocardial damage, perhaps permanent, long after the initial acute pericarditis.

CASE REPORTS

Case 1. A 57 year old white male executive was admitted to the Veterans Hospital, White River Junction, Vermont, on April 30, 1948, because of pain in the chest and fever. Three weeks prior to admission he had noted the gradual onset of a dull, aching, nonradiating substernal pain which was partially relieved when he lay prone. There was fever to 101° F. daily. The pain persisted for one week and then dis-

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From the Medical Service, Veterans Hospital, White River Junction, Vermont.
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appeared, but the fever continued until admission. The patient had had a head cold, without sore throat or cough, one month before the onset of illness. There was no history of rheumatic fever or equivalents, or of tuberculosis. The patient had worked in a granite quarry as a youth. Physical examination on admission revealed the temperature to be 99° F.; pulse, 100; blood pressure, 130 mm. Hg systolic and 80 mm. diastolic. The pharynx was normal, there was no venous distention, and the lungs were clear and resonant. The cardiac apical impulse was palpable 10.5 cm. to the left of the midline. The rhythm was regular. There was a grade I apical systolic murmur, and a loud pericardial friction rub was heard at the lower left sternal border. There was a patch of lichen planus on the left leg. The remainder of the physical examination was negative.

The leukocyte count was 11,100, with 80 per cent neutrophils. The erythrocyte sedimentation rate was 100 mm./hr. (Westergren). A throat culture showed no hemolytic streptococci, and two blood cultures were sterile. The Vollmer patch test was positive. Urinalysis was negative. The chest roentgenogram showed moderate cardiac enlargement and a slight bilateral fibrosis, thought to be consistent with pneumoconiosis. Serial electrocardiograms showed changes consistent with acute pericarditis (figure 1).

The patient improved gradually from the time of admission and was afebrile after 10 days. The friction rub persisted for three weeks. One month after admission, the size of the heart by roentgen-ray had returned to normal. However, when the patient was discharged on August 13 he was still dyspneic on walking about the corridor and had a persistent tachycardia of 100 to 110 beats per minute at rest. His sedimentation rate was 35 mm./hr., and in the electrocardiogram (figure 1), T_1 was inverted and T–V_6 isoelectric. Seven months after the onset of his illness (October 18), he was seen in a follow-up examination and still complained of dyspnea on exertion. The pulse was 100 at rest, with the remainder of the physical examination negative. The sedimentation rate was 39 mm./hr., and in the electrocardiogram (figure 1) T_1 was isoelectric. Two years after the onset of his illness (April, 1950), he was asymptomatic and working. The physical examination was negative and the heart was not enlarged by roentgen-ray. However, his electrocardiogram (not reproduced) showed the pattern of left ventricular hypertrophy,[16] with R–V_6 measuring 47 mm. and the sum of R–V_6 and S–V_1 equal to 42 mm.

Case 2. A 52 year old farmer was admitted to the Veterans Hospital on August 30, 1947. Five weeks before admission he had noted while eating a sudden, severe, knifelike, nonradiating substernal pain, aggravated by bending forward and partially relieved by sitting erect with his shoulders back. There were dyspnea and profuse sweating, and the patient collapsed while trying to reach his bed. The pain was severe for three days and persisted as a dull substernal ache for six weeks. During the second week of illness, his physician noted a pericardial friction rub and fever, both of which findings were present on admission on the thirty-third day of illness. There had been no history of upper respiratory infection or of rheumatic fever. A hired man who had worked for the patient six years previously was supposed to have died of tuberculosis subsequently.

Physical examination on admission revealed an apprehensive, slightly cyanotic white male appearing moderately ill. There was no dyspnea or cough. The temperature was 99.4° F.; pulse, 100; blood pressure, 118 mm. Hg systolic and 70 mm. diastolic; respirations, 20 per minute. The neck veins were engorged. The lungs were clear and resonant. The heart was not enlarged to percussion, and the apical impulse was not palpable. The heart sounds were distant, there was no murmur, and the rhythm was regular. A loud to-and-fro pericardial friction rub was heard over the entire precordium. The liver edge was palpable 4.0 cm. below the right costal

margin and was tender. There was no edema. The remainder of the examination was negative.

Laboratory Data: Hemoglobin, 15.8 gm.; white blood cell count, 13,800, with 81 per cent neutrophils. The sedimentation rate was 32 mm. per hr. Urinalysis was negative. The blood Kahn reaction was negative. Non-protein-nitrogen was 30 mg. per cent. The Vollmer patch test was negative. Four sputa were negative for acid-fast bacilli, and two blood cultures were sterile. Roentgenogram of the chest on September 2 (figure 2) was reported to show an enlarged "water bottle" cardiac shadow and clear lung fields. On fluoroscopy, cardiac pulsations were diminished

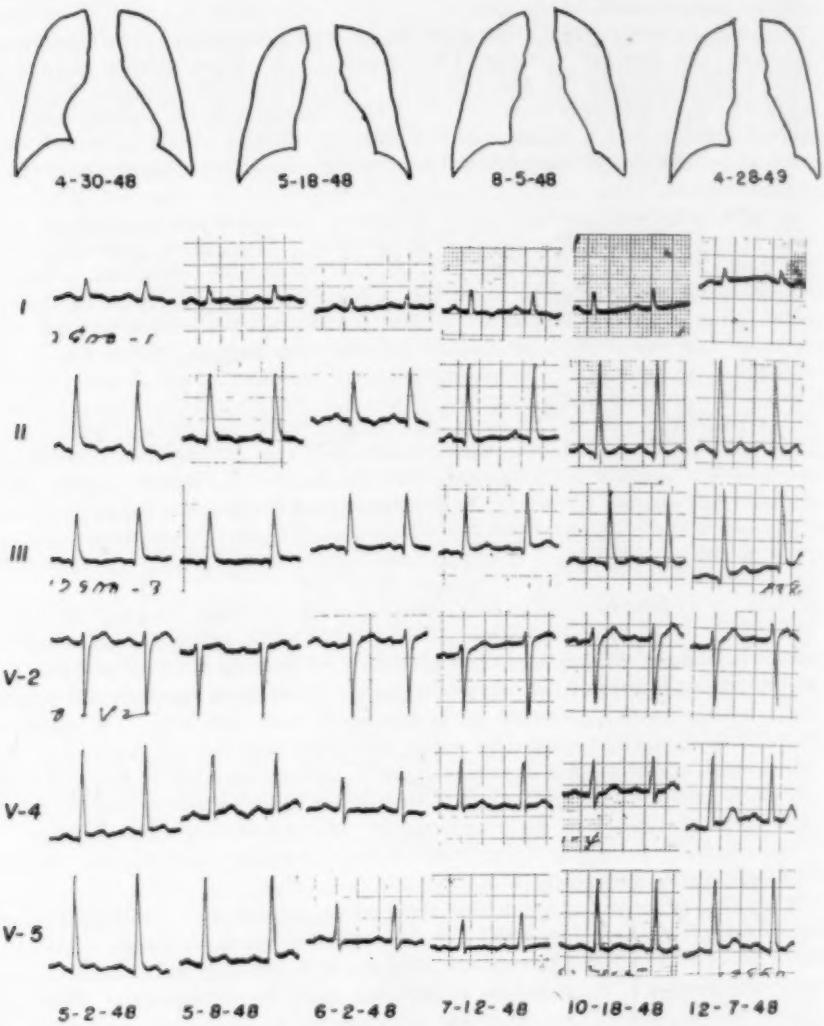

FIG. 1 (*Case 1*). Tracing of chest roentgenogram: Moderate cardiac enlargement (4/30/48) was present initially, with gradual return to normal size at 8/5/48. Electrocardiograms: ST–T changes were initially consistent with acute pericarditis (5/2/48 to 6/2/48). An abnormal T_1 was still present seven months later (12/7/48).

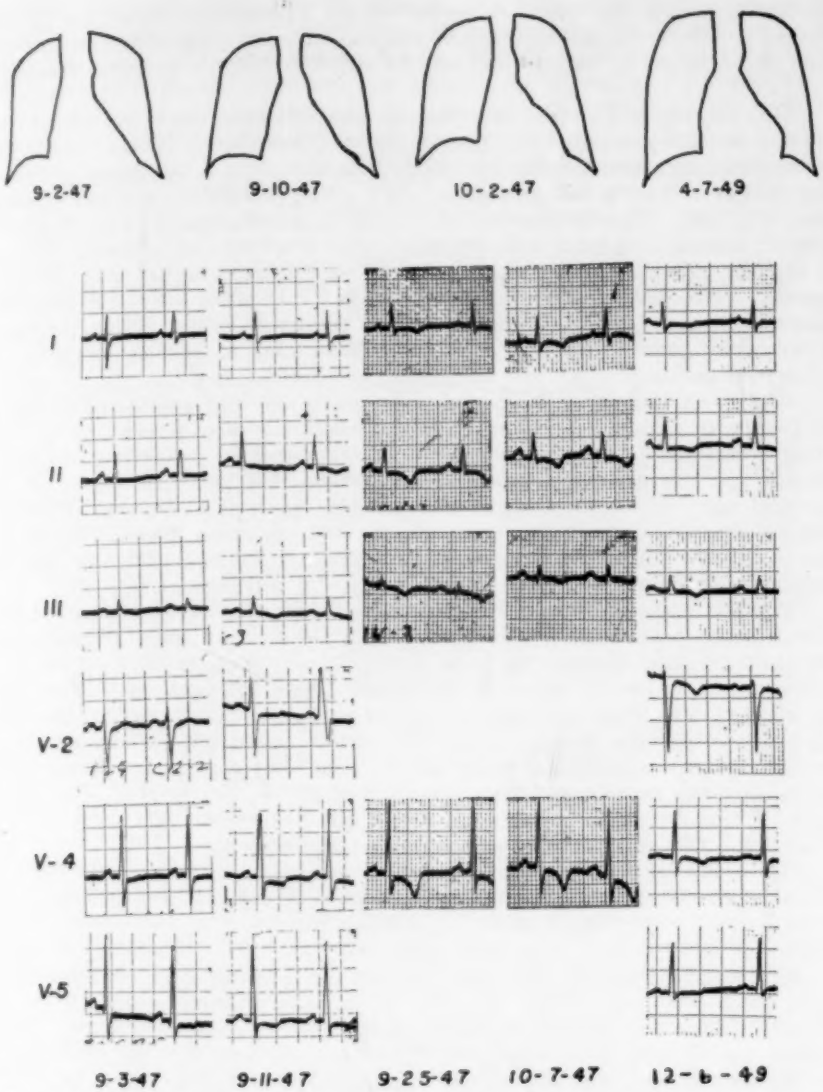

FIG. 2 (*Case 2*). Tracing of chest roentgenogram: Cardiac enlargement was present from 9/2/47 to 10/2/47. The cardiac silhouette on 4/7/49 was probably within normal limits. Electrocardiogram: There was no definite pattern. The abnormal T waves in standard leads and in V_5, V_4 and V_5, in the absence of QRS changes, could be produced by an acute pericarditis or diffuse myocardial disease.

and there was a significant change in cardiac contour as the patient's position was changed from erect to supine. Serial electrocardiograms showed a pattern consistent with pericarditis or diffuse myocardial involvement (figure 2).

It was thought that this patient had pericardial effusion, but no evidence of tamponade appeared and he improved rapidly, becoming afebrile on the fourteenth hospital day. The pericardial friction rub disappeared on the twenty-second day

coincidentally with the return to normal of the sedimentation rate. He was discharged on October 8, at which time he still had moderate dyspnea on exertion. The heart was enlarged by roentgen-ray and the electrocardiogram was abnormal (figure 2).

This patient has been seen on numerous occasions since discharge, the last being two and one-half years after the onset of illness (December 6, 1949). At this time, he was still unable to do anything more strenuous than drive a car because of dyspnea, easy fatigue and occasional episodes of dull aching substernal pain lasting several hours at a time. Physical examination showed the blood pressure to be 140 mm. Hg systolic; diastolic end point not obtainable. The heart was not enlarged, there was no murmur, and the rhythm was regular. The remainder of the examination was negative. The cardiac silhouette was normal in a roentgenogram of the chest. The electrocardiogram (figure 2) showed changes consistent with a diffuse involvement of the myocardium and was similar to the tracings taken at intervals during the preceding two years.

Case 3. A 52 year old laborer was admitted to the Veterans Hospital on March 15, 1949, with a history of sudden onset one month before of severe pain across the entire lower anterior chest. This pain was aggravated by swallowing and by respiration and was partially relieved by assumption of a supine position. The pain persisted until admission, though with steadily decreasing severity. Two weeks before admission, increasingly severe dyspnea and orthopnea began, although there was no edema. There was no history of tuberculosis, rheumatic fever or any recent respiratory infection.

Physical examination on admission revealed an acutely ill, orthopneic, confused, cyanotic white male. The temperature was 99.6° F. (rectal); pulse, 88; respirations, 34; blood pressure, 92 mm. Hg systolic and 70 mm. diastolic, with marked pulsus paradoxus. The neck veins were engorged. There was purulent discharge from the left ear. The lungs were clear except for a patch of dullness and tubular breathing at the left inferior scapular angle. The cardiac apical impulse was not palpable, but the heart was not enlarged to percussion. The heart sounds were of poor quality, the rhythm was regular, and there was no murmur or friction rub. The liver extended 7.0 cm. below the right costal margin and was tender. There was no edema or ascites. The remainder of the examination was negative.

The leukocyte count was 16,750, with 74 per cent neutrophils. The sedimentation rate was 7 mm./hr. on admission but rose to 67 mm./hr. one week later. The blood Kahn reaction was negative. Urinalysis showed a specific gravity of 1.018, a trace of albumin, and many casts (type not specified). The blood non-protein-nitrogen was 148 mg. per cent. Culture from the draining ear grew gram-negative rods, which were not further identified. Two blood cultures proved sterile. The venous pressure was 380 mm. of saline (normal 50 to 150 mm. of saline). Cardiac fluoroscopy 18 hours after admission showed marked rounding and enlargement of the cardiac shadow, with diminished pulsations and widening of the supracardiac shadow on change from erect to supine position.

This patient was believed to have acute pericarditis with effusion and cardiac tamponade. He was in critical condition for the first 48 hours, during which period the blood pressure ranged around 90 mm. Hg systolic and 70 mm. diastolic, and the mental confusion and peripheral congestion were unchanged. An attempted pericardial tap in the fifth left interspace at the midclavicular line was unsuccessful. However, improvement began on the third hospital day and was rapid thereafter, although the relation to the therapy with digitalis, mercurials and salt restriction was probably coincidental. The blood non-protein-nitrogen declined rapidly, reaching a level of 73 mg. per cent on the sixth hospital day and 32 mg. per cent on the thirteenth day. The urine, after the initial specimen, showed normal specific gravity, negative

sediment and an occasional trace of albumin. An intravenous pyelogram on the fiftieth day was normal. This temporary renal insufficiency was believed to be the result of the severe cardiac tamponade. On the thirty-third hospital day, three weeks after the blood non-protein-nitrogen had returned to normal levels, there was a

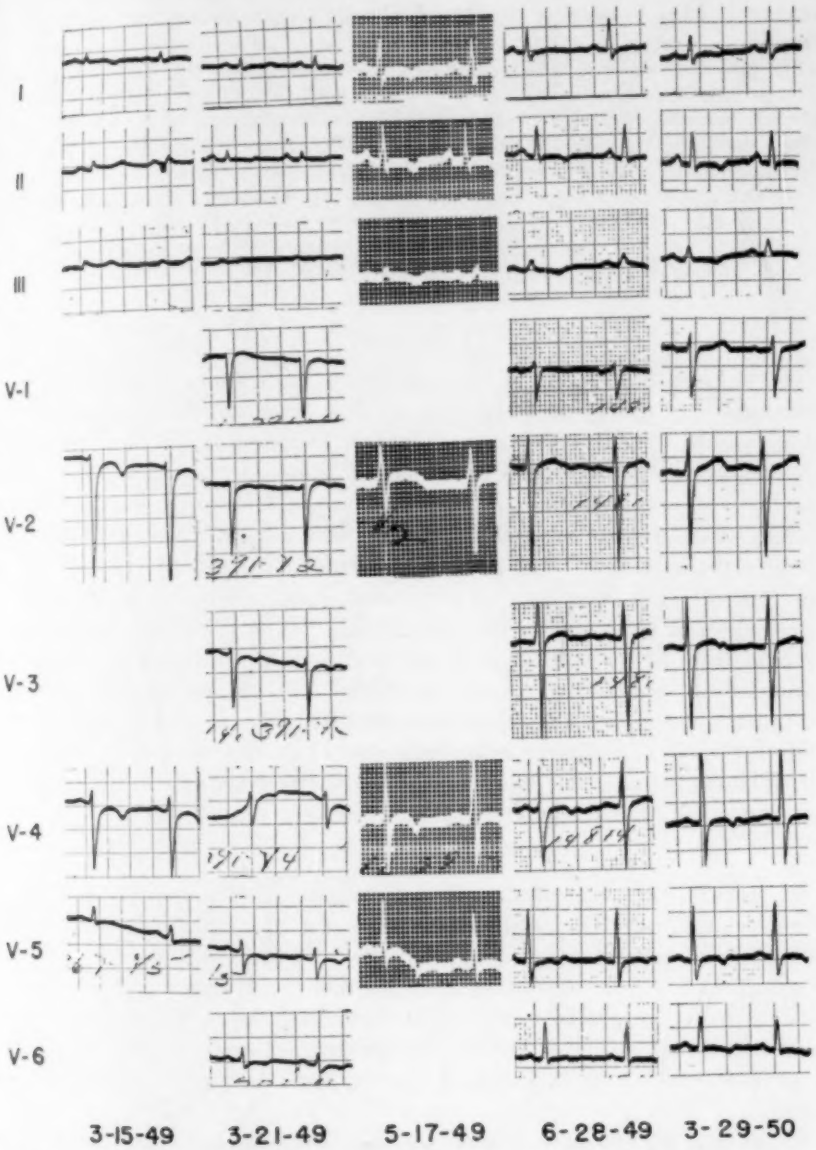

FIG. 3 (*Case 3*). Electrocardiograms: Progressive inversion of T waves, without QRS changes, consistent with pericarditis. Note low voltage in tracings of 3/15/49 and 3/21/49, when pericardial effusion was present. In the tracing of 3/29/50, the persistence of abnormal T waves in all standard leads and Leads V_3 to V_6 suggests widespread injury to the myocardium.

three-day recurrence of substernal pain without fever, and a pericardial friction rub was heard during this period. Following recovery from this brief relapse, further studies resulted in the incidental diagnosis of hemochromatosis, confirmed by biopsy of the liver. He was discharged on July 19, 1949, at which time he was dyspneic on walking but otherwise asymptomatic, and both physical examination and roentgen examination of the heart were negative. The electrocardiogram was still abnormal (figure 3).

The patient was seen in his home one year later. He had been working in a factory, wrapping packages, but was troubled by easy fatigue and dyspnea on walking at even a moderate pace. Physical examination showed the blood pressure to be 140/84, and pulse 90 after 10 minutes' rest. The lungs were clear. The cardiac apical impulse was palpable 1.5 cm. to the left of the midclavicular line. The rhythm was regular and there was no murmur. The liver was palpable 4.0 cm. below the costal margin. The examination was otherwise negative. Urinalysis was negative. The electrocardiogram (figure 3) still showed marked abnormality of the T waves consistent with widespread damage to the myocardium.

Comment

The uremia exhibited by this patient at admission was considered a manifestation of diminished renal blood flow resulting from a reduction in cardiac output produced by severe cardiac tamponade. The pathogenesis of this temporary renal insufficiency may be similar to that described by Van Slyke.[26] The rapid decline of the blood non-protein-nitrogen as the tamponade cleared and the absence of any further evidence of renal disease substantiated this concept. The acute recurrence of pericarditis at a time when renal function had been normal for three weeks showed conclusively that uremia was not the cause of the pericarditis. The possibility that deposits of hemosiderin in the myocardium and pericardium may have produced this clinical picture cannot be entirely excluded. Acute pericarditis occurring in a patient later found to have hemochromatosis has been reported elsewhere.[10 (case 4)] The clinical manifestations of hemochromatosis in our patient were slight, however, and the course of the acute illness was typical of acute nonspecific pericarditis.

Discussion

In recent years, correlation of electrocardiographic, pathologic and experimental findings has established the fact that nearly all cases of pericarditis are accompanied by damage to the myocardium, involving primarily the subepicardial layer of muscle, and that this involvement is responsible for the abnormality appearing in the electrocardiogram in these instances. It has also been shown that electrocardiographic changes do not occur when the pericardium alone is involved, as in some instances of uremic pericarditis.

Bellet and McMillan [17] observed extensive histologic involvement of the subepicardial myocardium in five cases of uremic or pneumococcal pericarditis in which the electrocardiogram had shown ST deviation during life. In four cases of pneumococcal or rheumatic pericarditis, in which

the electrocardiogram had shown ST deviation followed by T wave inversion, the same histologic pattern appeared. On the other hand, in seven cases of tuberculous or uremic pericarditis in which no electrocardiographic changes had appeared, the myocardium was found to be free of involvement at autopsy. The studies of Vander Veer and Norris [18] resulted in similar findings. Three cases of purulent pericarditis in which changes in the RT segment had appeared in the electrocardiogram proved to have subepicardial myocarditis histologically, while four cases of purulent pericarditis and two of uremic pericarditis, in which the electrocardiogram was normal, showed no myocardial involvement at autopsy. Similarly, in a case of rheumatic pericarditis with typical electrocardiographic pattern, Porte and Pardee [19] noted that the muscle lying beneath the area of pericarditis contained several regions of inflammatory reaction and foci of early scar formation. Perhaps the most direct evidence concerning the rôle of myocardial involvement in pericarditis appears in the observations of Hein and Reavis.[20] By electrocardiographic tracings before and during operation in a case of proved tuberculous constrictive pericarditis, they observed that the inverted T waves, present in the semidirect chest leads, were also present in the direct leads from the surface of the heart after the pericardium and thickened epicardium had been resected.

Experimentally, the introduction of saline, oil or other material into the pericardial sac has been shown to produce changes in the ST segments and T waves in the electrocardiogram.[21, 22, 23] In the case of nonirritant substances, it has been presumed that these changes are due to myocardial ischemia. This may be produced by interference with the blood supply to the superficial myocardium as a result of compression by the intrapericardial fluid under pressure. The observation that the magnitude of these changes was related to the degree of elevation of intrapericardial pressure,[23] and did not occur when the heart was merely bathed in saline under no pressure,[22] tends to confirm this presumption. When irritant substances are used and a sterile pericarditis is produced, the changes may be presumed due to involvement of the underlying myocardium as in clinical pericarditis.

From these observations it appears probable that, in a case of clinical pericarditis, electrocardiographic changes usually considered specific for pericarditis also signify myocardial involvement. If this is so, it seems possible that at times the myocarditis will be extensive enough to be manifest clinically. The probability of this course of events was noted 25 years ago by Vaquez,[24] who placed some importance on the muscular changes seen in acute pericarditis and attributed "the heart failure sometimes seen in pericarditis to this muscle change." In the cases here reported, the persistence of dyspnea and tachycardia, associated with electrocardiographic evidence of myocardial involvement, suggests that significant damage to the myocardium has occurred, even though frank congestive failure has not super-

vened. In case 3, where these abnormalities have persisted for two and one-half years, it may well be that they will prove permanent.

The possibility that the prolonged course noted in these patients was due to the development of constrictive pericarditis has been considered. In none of the three patients with acute nonspecific pericarditis reported above has there been any evidence of constriction by symptoms, physical examination or cardiac fluoroscopy. Furthermore, no cases of constrictive pericarditis as a sequel to this syndrome have been reported to date.

Electrocardiographic evidence of late myocardial involvement in three patients with acute nonspecific pericarditis, as well as clinical evidence of prolonged cardiac weakness in two of these patients, indicates that this syndrome is not entirely benign. It is of interest that a case has been reported elsewhere,[10 (case 8)] in which inverted T waves, interpreted as evidence of further myocardial damage, were present in the electrocardiogram taken eight months after the onset of pericarditis. As the syndrome of acute nonspecific pericarditis becomes more widely recognized and clearly defined, it seems probable that more instances will be observed in which significant injury to the myocardium takes place. It is not inconceivable that some instances of isolated (or "Fiedler's") myocarditis may actually have begun as acute nonspecific pericarditis; Covey's case of Fiedler's myocarditis[25] showed evidence of pericarditis at autopsy. The observations on the three cases reported here would indicate that it may be unwise to give an unequivocally good prognosis in patients having acute nonspecific pericarditis.

Summary

1. Evidence relating to the presence of myocardial involvement in pericarditis is reviewed.

2. Three cases of acute nonspecific pericarditis are reported in which clinical and electrocardiographic evidence of significant myocardial injury was present at seven months, one year and two and one-half years, respectively, after the onset of illness.

3. It is concluded that acute nonspecific pericarditis occasionally may be followed by prolonged, and perhaps permanent, myocardial injury.

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CASE REPORTS

ECZEMA VACCINATUM: REPORT OF A CASE TREATED WITH AUREOMYCIN *

By Bruce M. Esplin, M.D., *New York, N. Y.*

Edward Jenner's introduction to the medical world in 1798 of the possibility of a prophylactic vaccination for smallpox not only stimulated the establishment of the most effective known control of that disease but, in doing so, created an entirely new disease—eczema vaccinatum.

While it is a well known entity to the specially trained dermatologist and pediatrician, the average physician's knowledge of this disease is not commensurate with the importance of his potential rôle in its causation or with the relatively serious prognosis, once it is fully manifest. Part of this is undoubtedly attributable to its neglect in many of the older standard medical works and its scant mention even in recent medical texts. Also, the relative infrequency with which it is encountered has not fostered its wide recognition.

Its incidence during the intensive vaccination campaigns of the Nineteenth and early Twentieth Centuries has been reported [1] as approximately one in 20,000 to 40,000 cases. More recently, during the months of April and May, 1947, between five and six million people were vaccinated in New York City because of a small outbreak of smallpox in that city.[2] The incidence here was approximately one per 100,000 cases (38 cases collected).[3]

For many years following Kaposi's description in 1889 of "eczema herpetiformis" (later called Kaposi's varicelliform eruption), there was much confusion between eczema vaccinatum and this clinically similar, pathodynamically related disease. However, with the report of the isolation in three cases of the herpes simplex virus by Wenner [4] and others in 1944, thus confirming what previously had been only suspicion, Kaposi's varicelliform eruption was definitely established as a disseminated cutaneous herpes simplex and finally separated etiologically from eczema vaccinatum.

The following case, which did not occur during mass vaccinations, is illustrative of the common innocent production of the disease in a small family setting; it presents a typical course, with a few unusual features up to the time treatment was begun, and provides some interesting speculation on the efficacy of treatment now available.

Case Report

A white married woman, age 25, a private patient of Dr. George M. Lewis, had suffered from chronic disseminated neurodermatitis (atopic eczema) for most of her life, the most persistently involved areas being the flexor surfaces of the extremities.

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the face and the sides of the neck. In recent months her dermatitis had been well controlled through the use of oral antihistamine agents and bland local therapy. About 10 days following the smallpox vaccination of her 11 month old baby, she developed what appeared to be an acute exacerbation of her eczema, accompanied by a moderate cervical lymphadenopathy. She herself had been vaccinated for the first time two years previously, with a primary "vaccinia" reaction. The onset of high fever, chills, increase in the cervical lymphadenopathy and change in appearance of her skin lesions during the subsequent four days necessitated her admission to the hospital. Therapy during this period had been confined to topical cool saline compresses and a simple paste, oral antihistamines, and two intramuscular injections of penicillin by a local physician.

At the time of admission, examination revealed numerous round umbilicated vesicopustular lesions of varying sizes (3 mm. to 15 mm.), many of which had

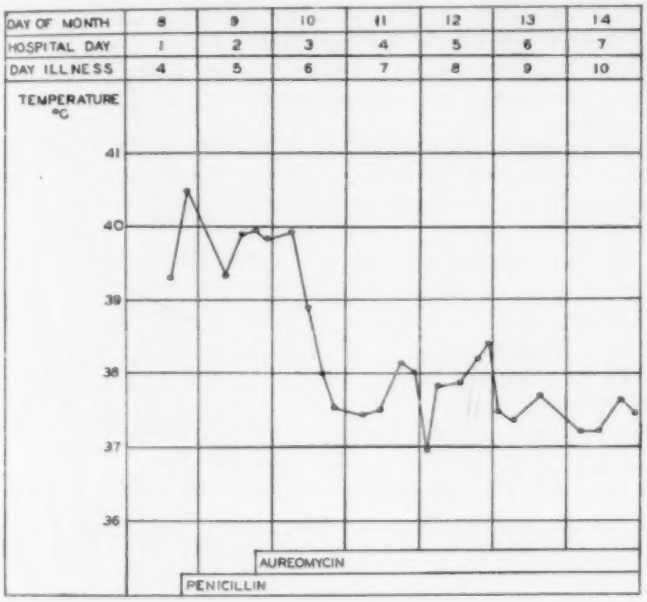

FIG. 1. Temperature course during the first seven days of hospitalization.

coalesced. These were mainly distributed in the previously eczematous areas, but were also sparsely scattered over the abdomen and chest. Cervical and axillary lymphadenopathy was marked. The right arm was erythematous, edematous, tense and tender. The temperature was 39.4° C., the pulse 90 and respirations 22. Except for the finding of a moderately enlarged liver and questionably enlarged spleen, the remainder of her physical examination was negative.

The results of laboratory examinations were: hemoglobin, 13.5 gm.; red blood cells, 3,500,000; white blood cells, 8,100; differential count: lymphocytes, 35; monocytes, 2; eosinophils, 1; basophils, 0; polymorphonuclears, 57 mature, 5 band; culture, negative. Stool examination and urinalysis were normal. Serum protein: 6.4 gm. per 100 c.c.; A/G, 3.8/2.6. Roentgenogram of the abdomen: hepatomegaly.

Following an initial rise to 40.4° C., the temperature remained at about 39.8° C. for two days, followed by a sudden fall on the third day to 37.6° C. Penicillin, in

doses of 400,000 U (300,000 U aqueous procaine penicillin plus 100,000 U aqueous penicillin G), was given twice daily throughout her hospital course. Aureomycin, 0.5 gm., was administered five times daily beginning at the end of the second day. Local therapy consisted of ice packs to the involved lymphadenitis, cool saline compresses and a bentonite paste. An oral antihistamine was continued in doses of 50 mg. every four hours. Chloral hydrate and Demerol were used for sedation. The skin lesions gradually resolved without scarring, and the lymphadenitis rapidly subsided following the fall of the temperature to normal. At no time during her illness did the patient have any severe generalized aching sensations or prostration, nor more than a moderate headache.

From the aspirated contents of one of the pustules, egg inoculations yielded a virus of the variolovaccinia group. Inoculations on a rabbit's cornea as well as cross-neutralization tests in that same animal strongly suggested that the virus was vaccinia.[5]

Figure 1 illustrates the temperature course during the first seven days of hospitalization and its relation to antibiotics received.

Discussion

Eczema vaccinatum is considered to be a form of generalized vaccinia in a person with a preëxisting dermatosis, usually atopic eczema, but occasionally seborrheic dermatitis, eczematized contact dermatitis, intertrigo, etc. Deliberate vaccination of such a person, or accidental exposure to another recently vaccinated, is the usual source of the virus. In the latter instance, inoculation may be the result of direct or indirect contact with the vaccination site at any stage of its development, or with secretions from the nasopharynx of the recently vaccinated person. Dissemination of the virus following its inoculation in the patient may take place through cutaneous contact in the eczematous areas, facilitated by the common concomitant itching, or it may spread by way of the blood stream with selective localization in these areas. It is well known that the vaccinia virus enters the general circulation soon after vaccination.[3]

In those cases following deliberate vaccination, the rash appears within a week (average, three days)[3] after the procedure. In those obtaining the virus through contact, a period of 16 to 20 days is most commonly noted between the vaccination of the contact and the appearance of suspicious lesions.[6]

Ross[1] has given an excellent description of the usual clinical course of the disease. The first suspicious sign is commonly a generalized nonspecific exacerbation of the underlying skin disease. Within three days lesions appear, with a rapid evolution from papules to vesicles to typical umbilicated pustules, usually limited to the eczematous areas. Later, some of these lesions may appear on noneczematous skin. Associated with the eruption is a temperature elevation to 104° F. to 105° F. (40° C. to 40.5° C.), which is sustained seven to ten days even in apparently uncomplicated cases, falling then by lysis. Regional lymphadenopathy, particularly associated with the most affected skin areas, is common. In younger children, hepatosplenomegaly is often encountered. Scarring is infrequent, and residuals of the rash gradually fade in the course of several months.

The reported mortality varies somewhat. In a series of 39 cases, McKhann and Ross[6] reported a mortality of 33 per cent, with two of the deaths occurring in patients over the age of 20. Greenberg[3] reports about a 5 per cent mortality

in 38 cases. Autopsies have shown only signs of generalized toxemia (cloudy swelling, fatty infiltrations of abdominal organs) and a terminal pneumonia.

This high mortality may be associated with the early age incidence of the disease, where previously unvaccinated children, in whom eczema is relatively common, comprise the largest group. In reviewing 41 cases in the literature, McKhann and Ross [6] found 19 in the first year of life, 16 between the ages of two and five, and six above 20 years, with an age range of two weeks to 42 years. In the more recent New York City series, three-fourths of the cases occurred in children under five years.[8] However, that no age group is exempt is readily substantiated by all reports.

It will be seen from the above discussion that this case of eczema vaccinatum in many respects presents typical features of the disease, including the method of inoculation, the incubation period, the development of the eruption and the clinical picture at the height of the illness. The occurrence of the disease in a 23 year old adult who had been successfully vaccinated two years before is somewhat unusual. Postvaccination immunity to smallpox is ordinarily considered to be present for at least five years.[7] However, complete immunity may not be so durable, and cases similar to this have been reported. Apparently eczema vaccinatum may occur not only in a previously vaccinated individual but even as a recurrence following a two year interval.[8]

Penicillin was administered to this patient on her first hospital day primarily in an effort to prevent secondary bacterial infection of her skin lesions, which might have led to scarring and a prolonged clinical course. This appeared to have little effect on her temperature course during the two days it was the sole antibiotic utilized. On the day following the addition of aureomycin to the treatment schedule there was a precipitous fall in temperature. This temperature decline occurred somewhat earlier in her course than would usually have been expected, and differed, too, from the described customary fall by lysis. Whether this unusual resolution of the acute phase of the disease was an expression of a partially immune state or was related, as it appeared, to the aureomycin administered, was of interest.

The dramatic effect of aureomycin on the rickettsia and larger viruses of the psittacosis-lymphopathia group is now well known. These viruses have a size range between 300 and 450 mu.[9] Although the vaccinia virus is one of the largest (236 mu., 135 to 252 mu.) of the remaining viruses, there has been as yet no report of conclusive evidence of activity of aureomycin on viruses of this smaller size. Reported favorable effects of aureomycin in some cases of herpes zoster,[10] and its apparent effect topically on cutaneous lesions of chickenpox, herpes zoster and herpes simplex,[11] are only suggestive of possible activity in this transitional range. Perry and Martineau [12] report a case of eczema vaccinatum in a child, with rapid recovery following aureomycin. However, Rose [13] in his studies has found aureomycin to be ineffective against the vaccinia virus. Two additional possible actions of aureomycin, other than a viricidal one, must be considered in evaluating this therapeutic response. A nonspecific antipyritic effect has been observed occasionally with aureomycin. There is a possibility, too, that a suppression of some nonpenicillin-sensitive secondary bacterial invaders, or a synergistic action with penicillin, may have played a rôle.

It is apparent that observations from a single case can only be suggestive; definitive conclusions must await further investigation and substantiation.

The smooth and noneventful recovery experienced by this patient should not deëmphasize the seriousness of eczema vaccinatum. Awareness of its potential existence should accompany each vaccination, and this procedure should be avoided in the presence of any extensive eczematous process in the individual under consideration, or in those in his immediate environment. In this era, smallpox vaccination is seldom more than an elective procedure, only rarely an emergency measure.

Summary

1. A case is reported of eczema vaccinatum in a previously vaccinated young adult white female.

2. The significant features of the disease and its apparent response to aureomycin therapy are discussed.

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SUBACUTE BACTERIAL ENDOCARDITIS PRESENTING AS A SUBARACHNOID HEMORRHAGE: REPORT OF A CASE WITH RECOVERY *

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The frequent occurrence of mycotic aneurysms developing in the cerebral arteries as a complication of subacute bacterial endocarditis is stressed by medical authorities.[1, 2, 3, 4] The paucity of reports in the recent medical literature [5, 6, 7, 8, 9, 10, 11] is striking, and suggests either that it is not as common as stressed or that its very frequency has deterred recent publications. Owing to the rarity of published cases, as pointed out by Starrs,[7] who published apparently the first report of subacute bacterial endocarditis presenting as subarachnoid hemorrhage with complete recovery, the history of a similar but earlier and heretofore unreported case is presented.

Case Report

A 41 year old white male store manager was admitted to Emory University Hospital on January 3, 1945, with the chief complaint of severe headache which had begun three weeks previously. The pain began in the right occipital region and subsequently radiated into both eyes. The day before admission he was awakened at 3:00 a.m. by the same complaint, which had become acutely severe and was associated with stiffness of his neck, roaring in his right ear and inability to move his left arm and leg. Also, at this time he noticed inability to speak intelligibly because of a "thick tongue." Review of systems revealed that he had been blind in his right eye since birth. Questioning for significant data in his past history revealed that for many years he had been troubled with constipation, postprandial epigastric distention and occasional nausea and vomiting. Because of this, he had gone to a nearby medical center in September, 1944, where examination showed a low-grade fever and a cardiac murmur thought to be on the basis of a patent interventricular septum. When an alpha hemolytic streptococcus was found on blood culture, the tentative diagnosis of subacute bacterial endocarditis was made. He returned to that hospital two months later for therapy. At that time daily blood cultures for two weeks were negative, so it was believed that the original organism was adventitious, and he was dismissed without treatment. After leaving that hospital he had intermittent fever, drenching night sweats, weakness, malaise and migratory arthritis involving the left hip, left wrist, left ankle and left tarsal joints. He noticed no chills but did have numbness, tenderness and aching of his fingertips at times.

Physical examination revealed an undernourished, chronically ill, cachectic white male, somewhat lethargic, with visible left facial weakness, left upper extremity weakness and slowness of speech. The temperature was 100° F.; pulse, 90; respirations, 18; blood pressure, 110 mm. Hg systolic and 80 mm. diastolic; and weight, 122 pounds. There were noticeable stiffness of his neck and a general semi-rigidity of his vertebral column. There was a petechia in the palm of his right hand and three

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petechial hemorrhages in the left antecubital fossa. There was generalized pallor of the skin. Ophthalmoscopic examination revealed in the lateral portion of the right fundus an area of pallor with pigment deposition, and there was a dilated vein in the medial portion. The left nerve head was not well visualized. No Roth's hemorrhages were seen. The oral cavity showed grade II sepsis. The chest was normal except for a few basilar atelectatic râles. Examination of the heart showed that the point of maximal impulse was in the fifth intercostal space, 9.5 cm. lateral to the midsternal line. Left border dullness was percussed 10.5 cm. lateral to the midline in the sixth interspace, 10 cm. in the fifth, 9 cm. in the fourth, and 5 cm. in

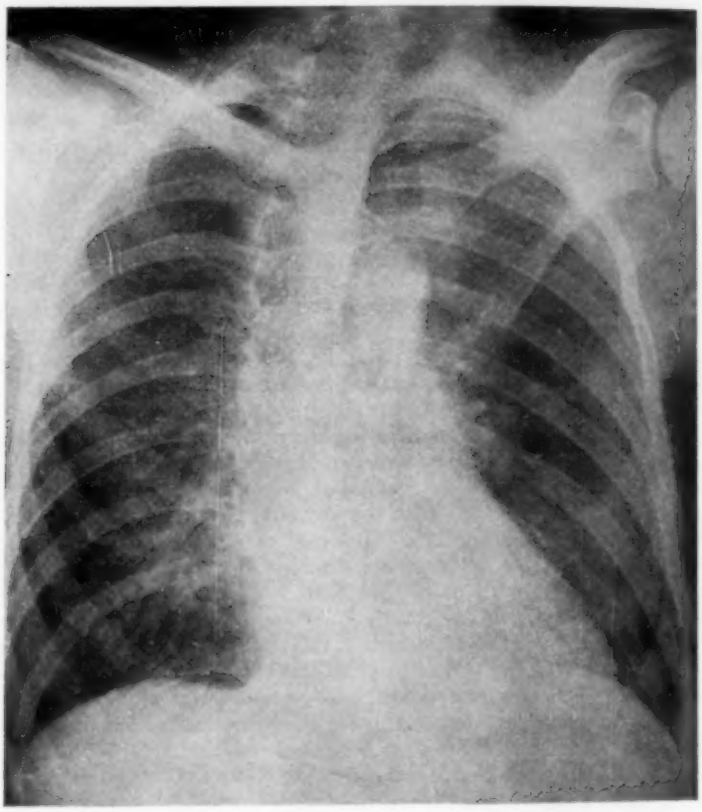

FIG. 1. Right anterior oblique, with barium swallow.

the third interspace. There was a harsh blowing precordial systolic murmur which did not transmit and which almost completely replaced the first sound. The pulmonic second sound was greatly accentuated. Splenic dullness was increased. The spleen was palpable at the costal margin and was soft and tender.

Significant laboratory findings consisted of 0 to 3 red blood cells per high power field in a catheterized urine specimen. Peripheral blood studies showed a red blood cell count of 4.07 million, white blood cell count of 9,650, and hemoglobin of 10.7 gm., or 65.6 per cent; the differential count showed a mild shift to the left. A blood culture was positive for alpha hemolytic streptococci, which were found to be

markedly inhibited by penicillin in high dilution. (We were not doing penicillin sensitivity tests at this time.) Lumbar puncture was done with an initial pressure of 195 mm. water; dynamics were normal. The fluid was grossly and uniformly bloody. Laboratory studies of the fluid showed 98 leukocytes per cu. mm. (6 per cent polymorphonuclears and 94 per cent lymphocytes), innumerable red blood cells, positive globulin and 67 mg. per cent total protein. No bacteria were seen on the smear, and cultures from the spinal fluid were negative. Stereoroentgenograms of the skull revealed no evidence of cranial pathology. Chest roentgenograms (figures 1 and 2), including a barium swallow, showed the heart enlarged and the esophagus indented by the aorta and displaced posteriorly by the heart in its lower third. Lung fields

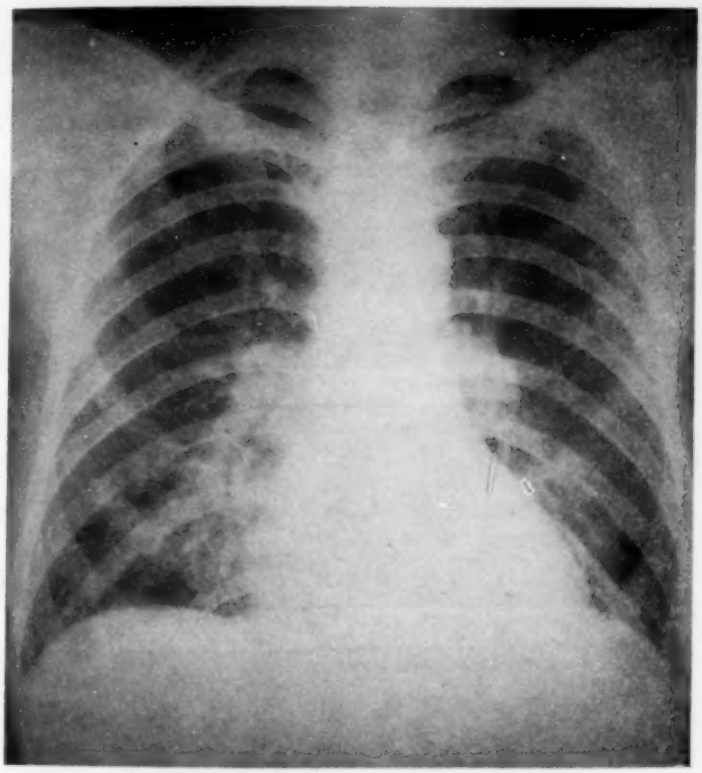

FIG. 2. Posteroanterior teleroentgenogram.

showed slight basal congestion. Electrocardiogram (figure 3) revealed left axis deviation, with a P–R interval of 0.16 second and QRS of 0.1 second. Stethocardiogram (figure 3) showed a holosystolic murmur, loudest at the mitral area, with a reduplicated second sound at the pulmonic and tricuspid areas.

On the basis of the above findings, a diagnosis was made of subacute bacterial endocarditis with a ruptured mycotic aneurysm of a branch of or the right middle cerebral artery and subarachnoid hemorrhage. The patient was placed on a high caloric diet and given two 500 c.c. transfusions of citrated whole blood; penicillin therapy consisting of 25,000 units intramuscularly every two hours was begun on January 11, 1945, the patient receiving a total amount of 5,000,000 units. On January

22, roentgen examinations of his teeth were made and the left inferior first molar was found to be pulpless and showed apical infection. This tooth was extracted. After three days of penicillin therapy, the patient began to notice marked subjective improvement. His temperature became normal, blood cultures became negative, and signs of subarachnoid hemorrhage and left hemiparesis cleared. His spleen remained palpable but was definitely less tender. Five blood cultures taken at intervals of four to five days were negative. His differential blood count became normal and

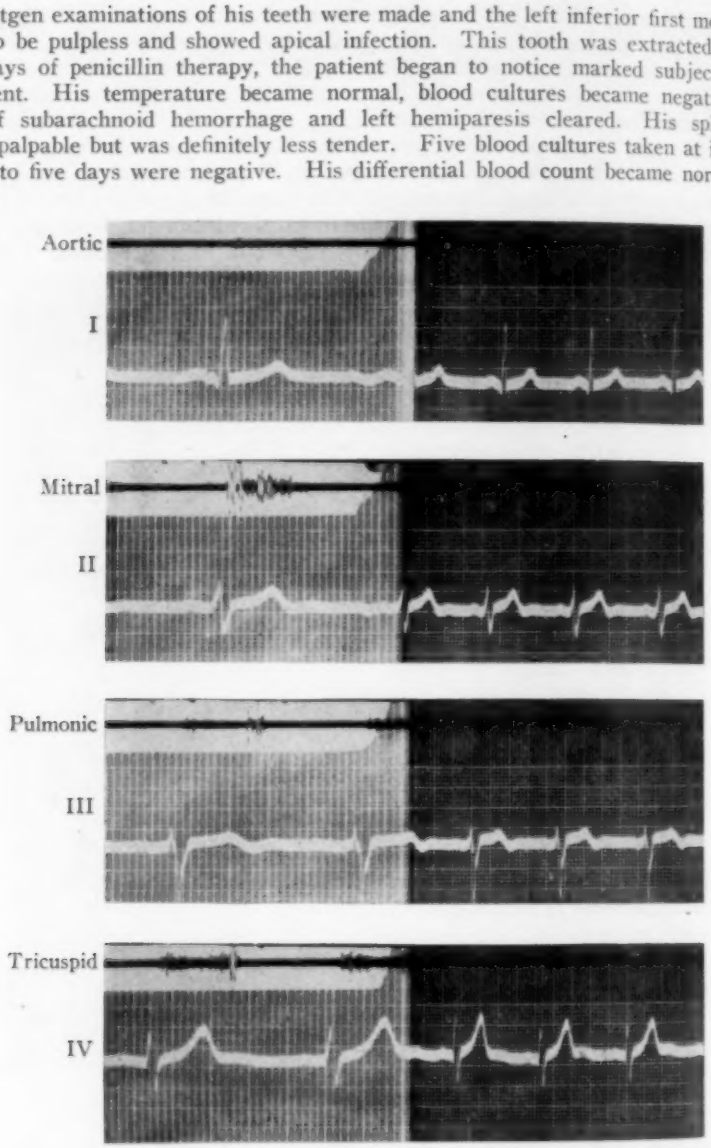

FIG. 3. Stethocardiogram and electrocardiogram.

his urine showed no red cells. On February 6, he was dismissed as probably cured, although the possibility of relapse was sensed since his splenomegaly persisted.

Following discharge, the patient remained asymptomatic for two days and then began to notice pain in his left calf which was accentuated by walking. This symptom became worse until the time of re-admission on February 13. He had no other complaints, was afebrile and showed no petechiae. He had gained about five pounds in weight but still appeared chronically ill. The spleen was only questionably

palpable. There was still cardiac enlargement and a loud, rough, systolic, grade III murmur was easily auscultated over the entire precordium. Examination of his extremities showed the left calf to be slightly but definitely larger than the right and tender on squeezing. Homans' sign was positive on the left, and there was tenderness to pressure in the left popliteal fossa. There was no pitting edema. The inguinal glands were not enlarged. There were no skin changes of lymphangitis, cellulitis or gangrene. Dorsalis pedis, posterior tibial, popliteal and femoral pulsations were present bilaterally. Other physical findings were essentially similar to those of his first admission. Blood and urine findings were not remarkable except for an occasional red blood cell in a centrifuged urine specimen. He had a red blood cell count of 4.3 million, hemoglobin of 12.2 gm. and white blood cell count of 5,850, with a normal differential count. Westergren sedimentation rate was 48 mm. in one hour. Blood cultures were taken and were negative. The tentative diagnosis was left deep femoral vein thrombophlebitis with possible recurrence of his previous endocarditis.

During his first hospital day he developed severe pain in his left lower chest anteriorly, accentuated by respiration and associated with dyspnea. There was no hemoptysis and roentgenograms were negative. It was believed that he had suffered a pulmonary embolus, although splenic infarction from an endocardial vegetation could not be ruled out. His temperature remained normal and there were no marked changes in pulse rate. Surgical consultation was obtained and on the following day a bilateral femoral vein ligation was performed under sodium pentothal and oxygen anesthesia. He withstood the procedure well but, following the operation, developed malaise, a low grade fever and night sweats.

Blood cultures were repeated on February 16, and were positive for *Streptococcus viridans* after four days' incubation. Following ligation of his femoral vein, sulfadiazine in full dosage was begun, in the hope that the organism might be responsive to sulfonamides. On February 25, penicillin was again administered intramuscularly every two hours with sulfadiazine until a total of 4,000,000 units was administered. He responded excellently to this therapy and was discharged asymptomatic on March 11. The cardiac murmur and splenomegaly, however, were still present.

About April 1 he again developed symptoms of endocarditis with positive blood culture. He was given 300,000 units of penicillin daily in divided doses until 8,000,000 units were received. Following this third course of penicillin, he remained in excellent health until the first week in July, when he began to notice malaise, vague abdominal discomfort, night sweats, anorexia, nocturnal fever, dyspnea and a sensation of precordial oppression. There were no cough, orthopnea, chest pain, hematuria, abdominal pain or other embolic phenomena. He was admitted to the hospital with an additional complaint of pain in his fingertips. Temperature was 99.2° F., pulse 110 and respirations 20. Examination showed definite hepatosplenomegaly. His cardiac murmur was louder and rougher than on previous admissions. Point of maximal impulse was in the fifth left intercostal space, 3 cm. lateral to the midclavicular line. A questionable systolic thrill was palpable at the apex. There were some fine dry râles in the posterior right apex following cough, but no moist râles were heard. No petechiae were seen. There was no swelling of his lower extremities, nor were there any suggestive signs of recurrent thrombophlebitis. Other physical findings were essentially similar to those of previous admissions.

Routine laboratory studies were not remarkable. There was no microscopic hematuria. Again, blood cultures were positive for alpha hemolytic streptococci.

On July 14, penicillin therapy was resumed at a level of 400,000 units daily by intramuscular drip. The penicillin was dissolved in 1,000 c.c. normal saline and given at the rate of 11 to 12 drops per minute.

As a result of this treatment, his symptoms rapidly disappeared. He became afebrile and gained five pounds in weight, and his sense of well-being returned. After

two weeks he was allowed up in a wheel chair, but the penicillin was continued at the same dosage 24 hours a day by slow drip into his thigh muscles. The needles were shifted every three to four days. There was no local reaction except for moderate tenderness. Every effort was made to keep these penicillin infusions continuous, and at the cessation of one clysis another was started immediately. This therapy was continued for 30 days, making a total dose of 12,000,000 units. His dyspnea, precordial oppression, night sweats, malaise and anorexia gradually disappeared. On July 21 his spleen and liver were no longer palpable. His temperature and pulse had already become normal. The cardiac findings persisted, apparently on the basis of irreversible valvular changes.

On August 19, 1945, he was discharged from the hospital.

He has been seen at frequent intervals since the last course of treatment, and has continued to remain free of symptoms and signs of recurrent endocarditis. At present, four years after his last course of penicillin, he remains well and his weight is 160 pounds. He has married and is actively engaged in work. He has no cardiac limitations in regard to his activity.

Discussion

The diagnosis of subarachnoid hemorrhage resulting from a mycotic aneurysm secondary to subacute bacterial endocarditis was suspected on admission because of the history and findings of heart murmur, splenomegaly, petechiae, stiff neck, left hemiparesis and bloody spinal fluid. There was an interval of eight days between the time of admission and the beginning of therapy because of the time required for culturing and identifying the infecting organism. Penicillin was begun with a daily dose of 300,000 units. The initial course of therapy with penicillin produced marked subjective and clinical improvement, with the clearing of the central nervous system symptoms and findings and also the symptoms and findings of subacute bacterial endocarditis, except for the persistence of splenomegaly and heart murmur. Further course of the patient, however, showed relapses, and only by increasing the daily dose of penicillin to 400,000 units over a period of 30 days did a cure of the subacute bacterial endocarditis result. Final cure was not produced until some seven months after the subarachnoid hemorrhage and approximately one year after the onset of symptoms of subacute bacterial endocarditis.

Starrs [7] in 1949 reported the first case of subacute bacterial endocarditis with subarachnoid hemorrhage with recovery that has been published. Starrs' patient was admitted to the Medical Service of the Ottawa City Hospital on July 12, 1945, in a semi-stuporous state. The patient had a slight degree of papilledema, nuchal rigidity and positive Kernig's sign, without other neurologic abnormalities. A lumbar puncture revealed bloody spinal fluid. It was not until the forty-fourth day that blood was withdrawn for culture and a nonhemolytic streptococcus isolated. On the fifty-fourth day it was positively identified as a *Streptococcus viridans*. On about the twelfth hospital day the patient was mentally clear but continued to have temperature elevation from 99.4 to 103° F. daily. He received no chemotherapy or antibiotic therapy until the forty-fourth day. It is interesting to note that by the thirty-fourth day, spinal fluid was normal even though no specific therapy had been instituted.

Paul, Bland and White,[9] in a survey of 44 cases of bacterial endocarditis treated with penicillin at the Massachusetts General Hospital from 1944 through 1946, reported two fatal cases due to subarachnoid and intracerebral hemorrhage

resulting from rupture of a mycotic aneurysm. Their first case was that of a 39 year old male who, on the tenth day of treatment, complained of severe headache and shortly thereafter lapsed into coma. Lumbar puncture revealed grossly bloody fluid. Paul, Bland and White stated, "Despite the ominous significance of this complication, he survived for another two and one-half weeks, finally succumbing to congestive heart failure." The other patient had just received a four weeks' course of therapy, with excellent results, when he suffered a massive subarachnoid and intracerebral hemorrhage and died within a few hours. Postmortem bacteriologic studies were all negative, and it was believed that the mycotic aneurysm has been sterilized but death had occurred from the resulting weakness in the arterial wall, with eventual rupture and fatal hemorrhage. The series of Paul, Bland and White included all forms of bacterial endocarditis, both the so-called acute and subacute.

Middleton and Burke [12] reviewed 80 cases of *Streptococcus viridans* endocarditis lenta, and of this group there was one case with a ruptured mycotic aneurysm of the basilar artery (autopsy).

Arteries of all sizes, from the minute unnamed branches in the brain to the aorta itself, may be involved in the formation of mycotic aneurysm. The formation of mycotic aneurysm is dependent on the enlargement of infected emboli on the endothelial lining, and from this point an inflammation of the vessel wall arises or, more frequently, the emboli are deposited in the vasa vasorum, thus producing focal arteritis with disintegration of the arterial wall and especially the internal elastic membrane. It would appear to the writer that recovery in his case and Starrs' was due to the fact that fortunately the site of the mycotic aneurysm with rupture and subarachnoid hemorrhage was a minute branch of one of the cerebral arteries. In the writer's case, it appeared to be due to rupture of one of the smaller branches of the right middle cerebral artery supplying the motor cortical area. Chances of recovery are, therefore, dependent upon the size and location of the cerebral artery involved, and adequate penicillin therapy at proper levels eventuating in a cure of the subacute bacterial endocarditis.

Conclusions

1. The reported incidence in the recent medical literature of subacute bacterial endocarditis complicated by subarachnoid hemorrhage is low. An incidence of approximately 5 per cent in a series of 44 cases of bacterial endocarditis was reported by Paul, Bland and White. This suggests that it occurs more frequently than is recorded in the medical literature. In Middleton and Burke's series of 80 cases there was an incidence of 1.2 per cent.

2. The history of a case of subacute bacterial endocarditis presenting as a subarachnoid hemorrhage is presented with the belief that this is the second recorded incidence of complete recovery from such an occurrence.

3. As in subarachnoid hemorrhage associated with arteriosclerosis and hypertension, complete recovery is dependent upon the size and location of the cerebral artery involved and adequate amounts of penicillin, according to the sensitivity of the infecting organism, to sterilize the infected valve.

4. Any patient who presents cerebral symptoms, heart murmur, fever, with or without splenomegaly, and petechiae should be suspected of having subacute bacterial endocarditis.

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THE RENAL MANIFESTATIONS OF PHEOCHROMOCYTOMA: REPORT OF A CASE *

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The dramatic occurrence of paroxysmal hypertension associated with headaches, nervousness, palpitation, nausea and vomiting is now a well known manifestation of pheochromocytoma. Pheochromocytoma is also increasingly recognized as a cause of persistently elevated blood pressure with attendant changes in the entire cardiovascular system. Not so well known, however, are the renal and urinary changes that may occur in this disease. To direct attention to these and their clinical importance, this case report is presented with a review of relevant literature.

Case Report

A 29-year old white male was first seen in the Clinic on September 1, 1943, for weakness and anorexia of about one week's duration, and "disturbed vision" of three to four months' duration. In May, 1943, his blood pressure had been 116 mm. Hg

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systolic and 58 mm. diastolic; urinalysis was negative. He was later seen by his family physician (May 21, 1943) because of severe headache, nausea and vomiting. His blood pressure then was 200/120. He was hospitalized and found to have a non-protein-nitrogen of 68, and albuminuria, hematuria and cylindruria. Urinary abnormalities gradually disappeared, and the blood pressure fell to 160/90. Late in July he had an episode of proteinuria for from 10 to 14 days, without concurrent symptoms. In August his vision became blurred and a few days later he was found to have advanced retinopathy. The urine was normal. When examined in the Clinic a few days later, he stated that he became dyspneic on moderate exertion and had had nocturia once nightly for several years.

Physical examination revealed a slender individual with average resting blood pressure of 208/135 mm. Hg and pulse rate of 116. There was a moderate pulmonary systolic murmur. No abdominal masses were palpable. Ophthalmologic examination revealed Grade IV eyegrounds. Basal metabolic rate was + 22 per cent. The urine had a specific gravity of 1.015, 4 plus albumin, was loaded with hyaline casts, and contained 3 red blood cells and 5 white blood cells per high power field. Hemoglobin was 13.5 gm. and blood urea 93 mg. per 100 c.c. and blood sugar (1 hour p.c.), 158. Urea clearance was 46 per cent of normal. During the two weeks after his return home from the Clinic, the urinary sediment gradually returned to normal and the albuminuria all but disappeared. His blood pressure fell from 190/120 to 156/94, but his fundi were unchanged.

In May, 1944, his blood pressure was 132/88, his urinary specific gravity 1.014, and microscopic examination negative.

He was admitted to the hospital on October 22, 1945, for reëvaluation of his condition. His blood pressure was constantly elevated and averaged 188/117. Intravenous pyelograms and heart size were normal. An electrocardiogram showed only a sinus tachycardia of 115 per minute. The only abnormality on electrophoretic analysis of plasma proteins was a beta-globulin of 1.48 gm. per 100 ml. (18.9 per cent of total proteins, normal 16 per cent). The Addis and Shevky's test showed the patient could concentrate urine to specific gravity of 1.021, with 0.58 gm. of urinary protein in 24 hours. Inulin-paraminohippurate determinations of kidney function revealed a renal plasma flow (RPF) of 772 c.c. per minute, glomerular filtration rate (GF) of 127 c.c. per minute, filtration fraction (FF) of 0.17, maximal tubular excretory capacity (Tm_{PAH}) of 43.0 mg. per minute per 1.73 sq. m., and RBF/Tm_{PAH} of 31.77. Patient was discharged from the hospital on October 30, 1945.

He was admitted to the hospital again on December 4, 1947. He stated that he had felt well since his previous hospital discharge and had been able to work daily until five or six weeks before admission, when his weakness returned. He had lost seven and one-half pounds, and had noted occasional objective vertigo during the previous one and a half months. Slight ankle edema appeared two days prior to admission. Nocturia had occurred four to five times nightly since 1943, with occasional urgency. Albumin had been found in the urine whenever it was examined during that time and had increased six weeks before admission.

On physical examination, blood pressure was 200/140 and pulse rate 88. Fundi showed Grade II constriction and Grade I sclerosis of the retinal vessels, one large recent hemorrhage, old retinal scarring bilaterally and mild retinal edema, but no papilledema. The heart was slightly enlarged to percussion, with an intermittent gallop rhythm, a Grade II systolic apical murmur, and A_2 equal to P_2. The liver was palpable 2 cm. below the costal margin and slightly tender on inspiration. No other organs or masses were palpated. There was Grade I pitting edema of the feet. Laboratory examinations showed 5,960,000 red blood cells, hemoglobin 13.5 gm., and blood urea 30 mg. per 100 c.c. Urea clearance was 56 per cent of normal. An Addis and Shevky's examination showed a maximal urinary specific gravity of 1.019,

3.8 gm. of urinary protein in 24 hours, with 1,200,000 hyaline and granular casts, 4,000,000 red blood cells and 3,000,000 white blood cells. The electrocardiogram was normal; cardiac enlargement was estimated as 20 per cent by roentgen-ray. Electrophoretic analysis showed 9.1 gm. total protein per 100 c.c. of plasma, albumin of 4.28 gm., and beta globulin of 2.18 (24 per cent of total). Renal plasma flow was 386 c.c. and glomerular filtration rate 77 c.c. per minute; FF was 0.20; Tm_{PAH} 55.5 mg. per minute per 1.73 sq. m., and RBF/Tm, 13.4. During his six-day hospital stay, his blood pressure averaged 193/120 and his pulse rate 96. He was discharged on December 10, 1947.

The patient died from a cerebral vascular accident on February 5, 1948, and the pertinent autopsy findings as reported by Dr. M. P. Hunter, Springfield, Ohio City Hospital are as follows:

The heart was generally enlarged and weighed 541 gm. The left ventricular wall measured 22 mm. in thickness; the coronary arteries, aorta and pulmonary artery were negative. The kidneys were of normal size and together weighed approximately

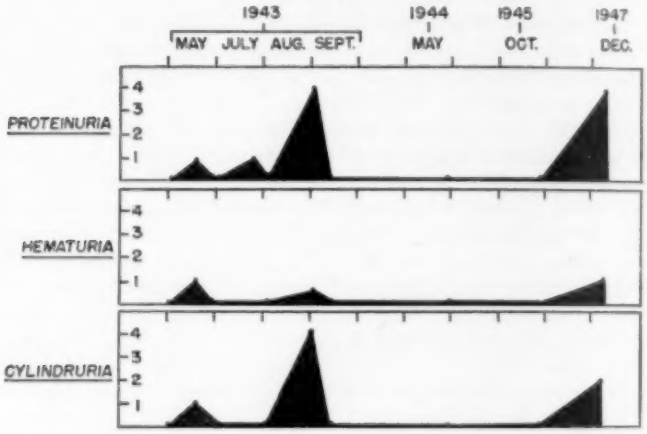

FIG. 1. Cyclic nature of urinary findings in case of R. Mc.

300 gm. The capsules stripped easily and the surfaces were smooth. The pelves and the mucosa were negative. The left adrenal was normal in size and gross appearance. The right adrenal was replaced by a well encapsulated, oval-shaped tumor, 8.5 by 6.0 cm., which when sectioned was brownish-tan in color. The brain weighed 1,471 gm. and revealed a right parietal lobe hemorrhage 7 cm. in diameter.

Microscopic examination of the tumor confirmed the gross diagnosis of pheochromocytoma. On examination of the kidneys, "the arteries show marked thickening of the muscles of their walls. There are quite a few hyalinized glomeruli and atrophy of their associated tubules which are replaced by fibrous tissue infiltrated by many lymphocytes."

DISCUSSION

The moderate retinal arteriolar sclerosis with the perivascular scarring, the remittent fundal and physical changes, the maximal concentrating ability of 1.021, the proteinuria, the slightly decreased filtration rate and the decreased Tm_{PAH} led us to believe that this patient probably had an early chronic glomerular nephritis. The labile blood pressure was thought to be consistent with this diag-

nosis. The increased beta-globulin is consistent with severe generalized vascular disease (Lewis and Page). When the true nature of the disease finally became apparent, it was thought that a review of previously reported cases with outstanding renal manifestations would be of value. The reports are summarized in table 1.

TABLE I

Author	Albuminuria	Hematuria	Cylindruria	Kidney Function	Renal Operative or Necropsy Findings	Remarks
Frankel[1]	Present		Few		Pelvic hemorrhages	
Labbé et al.[3]	Slight and variable			Anuria during crises. Blood urea 1.72 gm.	Necrotic areas in region of convoluted tubules	Postulated focal renal ischemia
Biebl and Wichels[4]	Present	Microscopic			Moderate medial hyaline degeneration of arterioles	Antemortem diagnosis of chronic atrophy of kidneys
Wichels and Biebl[5]	2+	Present	Numerous granular and hyaline casts	Serum nitrogen 65 mg. %	Normal	Antemortem diagnosis of chronic atrophy of kidneys
Rabin[6]					Infarcted glomeruli with necrosis of associated tubular epithelium. Arteriosclerosis	Felt arteriosclerosis due to mechanical effect of hypertension
Labbé et al.[7]	1–2 gm./liter			Azotemia: 0.6–0.7 gm./liter	"Chronic nephritis with slight glomerular sclerosis."	Probably not a true glomerulonephritis
Paul[8]	3%	Fine and large granular			Granular surfaces with narrowed cortex	The nephrosclerosis alone could account for findings
McKenna and Hines[9]	None	None	None	PSP 5% in 15 min. right kidney; 25% left	Superior pole right kidney compressed to one-half size lower pole.	Right pheochromocytoma and kidney removed
Kremer[10]	0 to 2+	None	Hyaline and granular casts	PSP fell from 75% to 30%	Infarcts, arteriosclerosis, thrombosis	Diagnosed chronic diffuse nephritis
Nuzum and Dalton[12]	Slight trace			Urea clearance 56%. Normal PSP excretion		
McCullagh and Engel[13]	Trace	Rare	None	Urea clearance 147% and 125% normal; 1½ yr. later 140% and 130% normal		Authors believe tumors stimulate kidneys to increased function
McCullagh and Engel[13]	Trace			160% normal urea clearance	Grossly and microscopically normal	
Hyman and Mencher[14]	3+	Present	Present			Urine regularly abnormal during an attack
Thorn et al.[15]	Slight trace	Occasional	Hyaline and granular casts	PSP: 25% excretion 15 min.; 50%, 2 hours		Clinical picture of malignant hypertension
Spatt and Grayzel[16]	2+		2+			No evidence of kidney damage following removal of tumor

Of interest is the report of Wiesel,[2] who found advanced medial arteriosclerosis similar to that produced with adrenalin by Josué in a two and one-half year old child who had a chromaffin tumor of the adrenal gland.

Kremer [10] described an interesting case of a 14 year old girl who was first seen in 1928 for dyspnea and cough. The urine specific gravity varied from

1.010 to 1.025 and albumin from 0 to 2 plus. There was an occasional hyaline cast. Blood pressure was normal. In November, 1929, blood urea nitrogen was 15 mg. per cent, phenolsulfonphthalein, 50 per cent excreted in one hour and 25 per cent in the second hour, a total of 75 per cent. She was discharged with a diagnosis of parenchymatous nephritis. In March, 1931, her urine showed hyaline and granular casts. She was re-admitted to the hospital in June, 1932, in stupor, with facial and peripheral edema and a blood pressure of 130/110. Fundus examination showed a "nephritic retinitis with arteriosclerosis incident to hypertension. There was bilateral atrophy of the optic nerve." Blood urea nitrogen was 14 mg. and creatinine 1.4 mg. per 100 c.c. In October, 1933, the urine specific gravity was 1.028. Eye grounds revealed old and new retinal hemorrhages. A diagnosis of chronic diffuse nephritis with hypertension was made. The blood pressure was 206/152 on the fourth admission in November, 1934. Urine specific gravity was 1.016 to 1.029, albumin 1 to 2 plus; there was an occasional granular cast, but no red blood cells. Phenolsulfonphthalein at this time was 10 per cent in the first hour and 20 per cent in the second hour, a total of 30 per cent. Blood urea nitrogen was 9 mg. per 100 c.c. The patient died suddenly with pulmonary edema. At autopsy the kidneys weighed 150 gm. each. The capsules were thin and stripped with ease, leaving a smooth surface. Cortex was of normal width. There were moderate atherosclerosis of the aorta and a marked generalized sclerosis. "In the kidneys there were recent anemic infarcts, arteriolar and intraglomerular hyaline thrombosis, severe tubular hyalinization and mild eccentric thickening of the intima of the renal arteries." A paraganglioma was found in each adrenal gland.

Of the 18 cases reviewed by Howard and Barker,[11] the urine between attacks was normal in nine; there was intermittent proteinuria regardless of attacks in three, and persistent proteinuria in six, five of whom had persistent hypertension. Non-protein-nitrogen or urea was elevated in four out of 12 at some time during the course of their disease.

MacKeith [15] in a recent review states that "during the attack there may be anuria or oliguria with albumin and casts in the urine, and azotemia, which may exceed 150 mg. urea per 100 c.c. Hyperglycemia and glycosuria are common." These findings "may vary remarkably independently of the patient's symptoms."

Green [17] reported a case in which the phenolsulfonphthalein (one hour) rose from 29 per cent before operative removal of the tumor to 70 per cent after. There was a trace to 1 plus albuminuria. He reviewed 50 case reports of pheochromocytoma, of which 37 showed persistent hypertension. Altered renal function was observed in 24 of the 37 chronic cases; albuminuria, intermittent or constant, in 20; subnormal phenolsulfonphthalein in 11; abnormal sediments in 10 and azotemia in two. Of four urea clearances reported, two were normal and two were increased. In the paroxysmal hypertensive group, there was renal dysfunction of some type in only five of 14 cases between paroxysms. Of 16 chronic hypertensive patients who came to autopsy, nine had no significant renal disease. There was mild to severe nephrosclerosis in seven. In general, the symptoms lasted longer, retinitis was more intense, renal functional changes were more frequent, diastolic pressure was higher and heart weight greater in cases with renal disease. The neoplasm was removed from 22 patients with chronic hypertension, of whom 13 had disturbed kidney function. Of these 13, there was

improvement in five, as manifested by increased concentrating power and phenolsulfonphthalein, decreased albuminuria and disappearance of abnormal sediments.

The 20-year old girl with severe diabetes reported by Goldner and observed by some of us [18] had normal kidney function between her paroxysms of hypertension. The following values were obtained preoperatively in May, 1944: RBF 1373 c.c./min., GF 130 c.c./min., FF 0.17, Tm_D 52.6 mg./min./1.73 sq. m., HD/Tm_D 26.1, mean arterial pressure 90 mm. Hg.

The mechanism of the renal changes and the consequent proteinuria, cylindruria and hematuria is not definitely known. It has been supposed that the symptoms arising from these tumors are the result of the production and release of adrenalin and nor-adrenalin. No one, however, has found increased amounts of circulating adrenalin in the blood of persistently hypertensive individuals or between paroxysms superimposed upon a persistent hypertension. It is likely that patients with paroxysmal phenomena will develop persistent hypertension with protein, casts and red blood cells in the urine if the pheochromocytoma is not removed.

In our case, there were marked changes in the kidney function between October, 1945, and December, 1947. Renal blood flow greatly decreased, along with a rise in estimated efferent arteriolar resistance to five times the former value. That there was a marked ischemia of the parenchyma was indicated in the reduction of the ratio of blood flow to Tm from 31.7 to 13.4. These changes are consistent with those produced during acute experiments with adrenalin on normal human beings. The reduction by one-third of inulin clearance might be attributed to the increased number of hyalinized glomeruli, but the unchanged Tm_{PAH} shows that a specific tubular function was not concurrently affected and suggests that the functioning nephrons remained about the same. A more plausible cause for the change in filtration rate would be increased efferent arteriolar resistance.

From the case here presented and many of those cited, it is apparent that urinary abnormalities may occur persistently or paroxysmally without subjective symptoms. This points to the existence of "subclinical" attacks with objective urinary manifestations. As the disease progresses untreated, it eventually reaches the stage where abnormal findings are constantly present.

Renal excretory functions may be normal, above normal or greatly depressed. The marked renal vasoconstriction in paroxysmal hypertensive crises may result in anoxia of the capillary tufts and of the tubular epithelium. The reversibly damaged vascular walls and tubules then permit the proteinuria, hematuria and cylindruria. With the development of chronic hypertension and the increased arteriosclerosis, more permanent damage occurs and the functional efficiency of the kidney markedly decreases. The plasma flow is reduced, the filtration fraction and vascular resistance rise and the RBF/Tm falls.

In retrospect, the normal red blood cell count and relatively normal hemoglobin, the hyperproteinemia with a beta-globulin of 24 per cent of the total protein and the episodic nature of the early stages of the disease pointed away from chronic glomerulonephritis. It would appear then that a "paroxysmal nephritis," as demonstrated in the accompanying graph, associated with paroxysmal hypertension, should point to the presence of an adrenal medullary tumor. If the disease is allowed to progress, the hypertension may become persistent and the renal manifestations may in some respects simulate those of a chronic glomerulonephritis.

Summary

A case of pheochromocytoma of the adrenal gland that was diagnosed as glomerulonephritis is reported, and case reports of other patients with similar findings are reviewed. The effect of such tumors upon kidney function is described and a possible explanation is presented. Paroxysmal nephropathy may be an outstanding manifestation of the presence of adrenal medullary tumors.

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CYCLIC ACUTE AGRANULOCYTOSIS: REPORT OF A CASE, WITH IMPROVEMENT AFTER SPLENECTOMY *

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SINGLE episodes of acute agranulocytosis caused by drugs, poisons, roentgen-ray or ionizing radiation are common, and their pathology and clinical course are well known. Transient neutropenia occurs following many infectious diseases, and chronic neutropenia is present in cases of bone marrow hypoplasia as well as in conditions associated with infiltration of the bone marrow.

Since the concept of hypersplenism was first advanced by Wiseman and Doan,[1] a variety of clinical syndromes has been described in which either acute or chronic neutropenia or a combination of both phases occurs as a selective entity or as part of a pancytopenia affecting all elements produced in the bone marrow.

True spontaneous agranulocytosis occurring in cycles has rarely been described. The reported cases are characterized by episodes of partial or complete disappearance of neutrophil cells from the blood at regular intervals of about three weeks. Fever, oral ulcerations, abdominal pain and varying degrees of prostration have closely paralleled cyclic fluctuations in the peripheral blood picture.

Both sexes and all ages are represented, and the duration has been from months to years. In some patients the disease has run an intermittent course.

In two articles Reimann [2, 3] briefly discusses several reported cases of cyclic neutropenia under the general heading of periodic disease. Later, Reimann and de Berardinis [4] describe in detail a case of their own and review the data in 15 other cases of periodic cyclic neutropenia previously published. This report also includes a case by Owren [5] and one by Fullerton and Duguid,[6] both published in 1949.

An additional case is found in a report on the results of splenectomy in primary splenic panhematocytopenia by Heinle and Holden.[7] In their patient a mild cyclic neutropenia, associated with anemia and thrombocytopenia, occurred at three to four month intervals over a period of years.

Stephens and Lawrence [8] report a patient in whom the cyclic course terminated spontaneously, after which a normal blood picture was maintained.

Therapy with penicillin has now effectively supplanted sulfonamides in the management of sepsis. Splenectomy has lately been tried in an attempt to alter the course of the disease.

The following is a report of such a case.

CASE REPORT

A 64 year old white woman was admitted to St. Peter's General Hospital on July 20, 1948, for treatment of an ischiorectal abscess.

History of Present Illness: While on a vacation she developed a fecal impaction which was removed manually, and the patient was then treated with enemas. No medication other than mineral oil was given. The rectal infection which followed lasted four days.

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Past History: The patient's general health had always been good. She had had a mastoidectomy complicated by erysipelas 20 years before, and a bilateral saphenous vein ligation in 1945. She had had five normal pregnancies: The menopause had occurred at the age of 47. She gave a history of occasional mild digestive upsets, attributed to gall bladder disease, together with chronic constipation of many years' duration. Roentgen-ray studies performed in 1942 were normal. Careful questioning failed to elicit any history of blood dyscrasia, drug consumption or symptoms that might be related to agranulocytosis. The family history was noncontributory.

Physical Examination: The patient was a robust woman, with good color, edentulous. Skin and mouth were normal. Blood pressure was 140 mm. Hg systolic and 70 mm. diastolic. The heart was normal except for a soft systolic apical murmur. The lungs were clear. The abdomen was soft and without any palpable splenic or hepatic enlargement. There was no enlarged lymph node. A vaginal examination proved normal. A large, left-sided ischiorectal abscess was found.

Course of Illness: On admission the blood count showed a leukopenia of 2,250, with 4 per cent neutrophils, but was otherwise normal. The temperature was 101.4° F., rose to 104° and subsided in 48 hours under penicillin therapy and drainage of the abscess, which healed rapidly. She received one pint of whole blood. The neutrophils increased rapidly and she was discharged on the seventh day, with a total leukocyte count of 2,700, of which 73 per cent were neutrophils. The patient was well for three months. Repeated blood counts averaged about 5,000 leukocytes, with a normal differential count. On October 25 she became ill with a sore throat, chills and fever. She had a severe ulcerative stomatitis, cervical adenitis and several pustular lesions on the scalp and hands. Blood studies showed a complete agranulocytosis. The patient was hospitalized and treated with penicillin, small blood transfusions and parenteral injections of folic acid.

The course of her illness was stormy, with severe sepsis and gangrenous ulcerations of the skin. The neutrophil count improved daily, however, and became normal within 10 days, followed by rapid healing of the oral lesions and gradual improvement of the skin lesions.

An interval of normality lasted for two months. In January, 1949, episodes of acute agranulocytosis began to recur, as illustrated in figure 1. Each attack was ushered in by malaise, chills, fever, ulcerative stomatitis and conjunctivitis, and lasted about one week. The onset of symptoms was always preceded by the total disappearance of neutrophils from the blood. Fall in temperature and healing of the oral lesions always followed closely the reappearance and rapid rise of neutrophils. It became evident very soon that the recurrences were of a cyclic character and appeared at intervals of 20 to 22 days. Thus it also became possible to predict their onset. Penicillin effectively controlled the severe sepsis and treatment was continued at home.

In March the edges of the spleen and liver became palpable. From that time the spleen grew larger and more tender with each attack, the swelling partially subsiding with recovery. After the tenth attack, because of progressive deterioration in the patient's condition and the increasing splenomegaly, splenectomy was performed on June 27, during an interval. For reasons to be discussed later, the operation was considered as a palliative measure only. The spleen weighed 670 gm. A biopsy specimen was taken from the slightly enlarged liver. A small and shrunken gall bladder contained stones but was not removed. The patient tolerated the procedure well. It is interesting to note (figure 1) that the predicted agranulocytosis occurred on the anticipated date after splenectomy, but was asymptomatic. The patient was receiving penicillin before and after her operation.

She was discharged on the seventeenth postoperative day with a normal blood count. The chart shows her subsequent course: rapid improvement in her general

condition and gain in weight through a prolonged asymptomatic period, during which fluctuating neutropenia and agranulocytosis were discernible only on blood examination and required no medication. This favorable course has been interrupted by several short episodes of fever and mild upper respiratory symptoms, lasting one or two days and occurring at times when the neutrophil count was relatively satisfactory. As a precaution, several injections of penicillin were given each time. At present (eight months after operation), the neutropenic periods no longer occur every three weeks but appear at longer intervals.

Blood Studies: Numerous blood counts were performed and smears studied and compared during a 20 month period. Red blood cell counts varied from 3.75 to 5 million; hemoglobin from 12 to 14 gm., without any periodic fluctuation. Total white cell counts ranged from a low of 500 in some attacks to levels of 3,000 to 5,000

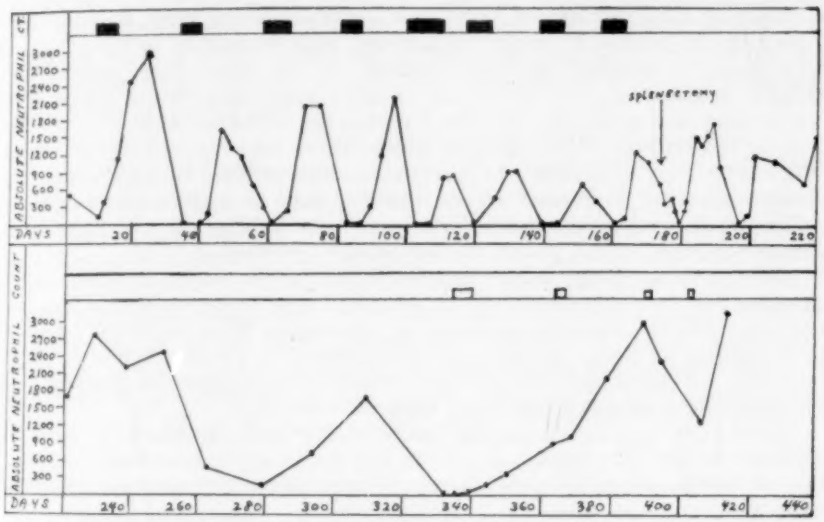

FIG. 1. Chart showing fluctuations in absolute neutrophil count per cu. mm. Dark blocks represent periods of fever, prostration, stomatitis; open blocks represent periods of fever only.

with recovery. Neutrophil counts are shown in figure 1. When the count declined, the neutrophils showed vacuolation of the cytoplasm and toxic granulations, with many degenerated cells in smears. Early in the recovery (especially with rapid rises), a few myelocytes appeared, and there was a distinct left shift. Basophils and eosinophils were unaffected.

Lymphocytes varied in number inversely with the neutrophil values. At times the monocyte levels became quite high during agranulocytic phases. This, however, was not consistent. It has been considered a good prognostic sign by some observers.

After the splenectomy a gradual rise in both total leukocyte and total neutrophil counts occurred. This has persisted with minor fluctuations, and several periods of agranulocytosis have occurred. Characteristic postsplenectomy changes are evident in blood films like those described by Singer,[9] namely, the appearance of target cells and Howell-Jolly bodies.

Platelet counts, which were constant and normal preoperatively at 298,000, rose slowly after splenectomy to reach a maximum of one million on the seventh day and

then returned to former levels, which are being maintained. The adhesive platelet index rose and fell similarly, a normal effect.

Bleeding and coagulation times and prothrombin levels were normal and remained unchanged. In a search for etiologic factors, repeated cultures, agglutination tests and roentgen-ray studies were all normal.

Bone Marrow Examinations: Sternal marrow aspirations were done during the acute agranulocytic phase, in intervening periods and after splenectomy. Estimated qualitatively, the marrow was sparse and appeared somewhat reduced in cellularity. However, erythropoiesis and megakaryocytic activity and maturation were normal at all times. During agranulocytosis, granulopoiesis was represented by a few myeloblasts and a proportionately greater number of promyelocytes and myelocytes. Mature forms were rare, and many basket cells and bare nuclei were present. There were both a depression and a maturation arrest at the promyelocyte-myelocyte level. This picture was reduplicated during separate attacks.

Preceding the appearance of neutrophils in the peripheral blood, the bone marrow showed a great increase in myelocytic activity, with maturation to the polymorphonuclear stage—a definitely leukemoid picture. In the intervening periods, with a peripheral neutropenia, there were still reduced granulopoiesis, as compared with other elements in the marrow, and also a persistence of the left shift.

After splenectomy, there appeared indications of improved granulocytic function in the marrow, and an increase in primitive reticulum cells. Though this is only a qualitative appraisal, it is based on the improved ratio of granulocyte to erythrocyte activity, the latter having remained fairly constant throughout. A leukemoid appearance persisted, but the peripheral neutropenia improved.

The appearance of the sternal marrow at the various stages would indicate that a selective and periodic depression of granulopoiesis occurred, with a maturation arrest preceding the total disappearance of neutrophils from the blood. This state was maintained for five or six days and was followed by a resumption of activity and progression of maturation, with a rapid release of cells from the marrow. Some myelocytes even appeared in the blood early in recovery.

The changes seen in this patient closely parallel those described by Owren [5] and Fullerton [6] in two very similar cases. Comparable changes have been described by others [10, 11, 12] as occurring in the marrow of toxic agranulocytosis induced by known agents.

Spleen and Liver Biopsy: Sections through the liver showed chronic pericholangiolitis. Grossly, the spleen was smoothly enlarged, weighing 670 gm. Microscopic sections showed extreme reticulum cell hyperplasia, with transformation of the pulp into miliary granuloma-like nodules. The pathologist remarked about the unique appearance of these nodules, and felt that they were the result of some proliferative stimulus of a possibly chronic infectious type. Efforts to discover an infection were unsuccessful. Sequestration or phagocytosis of leukocytes was not observed in the fixed sections.

In pathologic reports of spleens removed for neutropenia and panhematopenia, cyclic or otherwise, the universal finding has been a nonspecific follicular hyperplasia. In the present case, the spleen was assayed and found to have an extremely high content of thrombocytopen. This is a substance which can be extracted from the spleen and which produces a depression of megakaryocytic fragmentation and platelet formation in the marrow and results in thrombocytopenia.

Discussion

Reimann's [4] review discusses fully various investigations and theories concerning the etiology of cyclic neutropenia. The cause, however, is still unknown.

There is no finding in the present case which might help to clarify the problem. Although attempts to discover some endocrine relationship have been unsuccessful, the nature of the illness and its periodic selective influence on granulopoiesis are strongly suggestive of some such factor. Recent preliminary reports on ACTH have shown it to have definite hematologic effects, producing a rise in the neutrophil count. It has also been used successfully in controlling and causing remission in acute leukemia, an indication of its influence on granulocytic development.

The host of therapeutic agents used in the past in the treatment of acute agranulocytosis have all been of doubtful benefit. In this case, large doses of folic acid, given orally and parenterally, and also B_{12} were used empirically without effect. Small fresh blood transfusions were of value only as supportive treatment. Penicillin was consistently effective in controlling severe sepsis and in preventing the gangrenous ulcerations which are so frequent during the acute stage. Before the splenectomy was performed, some episodes were so severe that it is doubtful whether the patient would have survived without this antibiotic. Its use permitted effective and simple home management through the period illustrated in the chart (figure 1).

In recent years, cases of neutropenia have been subjected to splenectomy. In successive articles on hypersplenism, Doan [13, 14, 15] differentiates between primary splenic panhematocytopenia of familial or congenital origin, and the secondary type, in which splenomegaly is due to some constitutional process, such as Hodgkin's disease and leukemia. The total or selective cytopenic effect is attributed to a sequestration and excessive lysis of circulating blood elements within the pathologically functioning spleen. The bone marrow shows a compensatory hyperplasia of one or all elements. Splenectomy is curative in the primary type. The peripheral blood picture promptly and permanently returns to normal. The effect is only temporary in the secondary type, and splenectomy is contraindicated in the presence of a depressed or aplastic marrow.

Others (Dameshek [16, 17] and Hirschboeck [18]) have advanced the concept of an hormonal relationship in which the spleen controls the maturation and release of bone marrow elements. In hypersplenism, excessive hormonal production may inhibit the process either totally or selectively.

There is evidence for both points of view. In some cases,[19] the spleen has shown evidence of excessive cellular phagocytosis and lysis, whereas in others [7, 20] this could not be demonstrated. The adrenalin test appears of value in some cases. In a recent discussion, Kracke [21] broadens the indications for palliative splenectomy. Insofar as neutropenic states are concerned, the most striking results have occurred in cases also exhibiting anemia and thrombocytopenia and an active marrow.

However, an examination of case reports of cyclic agranulocytosis reveals no indication that hypersplenism is responsible for the periodic fluctuation. There is good evidence for assuming, however, as in the present case, that an overactive spleen does influence the severity and degree of neutropenia. In evaluating the results, a distinction must be made between cases showing normal or hyperplastic myeloid activity in the bone marrow and those in which it is depressed. Only a few of the cyclic cases have had splenectomy, and the operation either has been ineffective or has resulted in some improvement in the neutropenia.

In the present case, the appearance of the bone marrow was discouraging.

Because of the progressive downward course, it was felt that the enlarging spleen was an unfavorable factor, and that even a palliative result would be worthwhile. Fullerton's case with a favorable result had just been reported. The late 1949 publications had not yet appeared. The immediate effect of splenectomy in the present case was excellent, as shown by the subsequent clinical course. However, improvement in the neutrophil count was slow and was not consistently maintained. The cyclic pattern has been altered but still persists. It is remarkable how well severe neutropenia is tolerated. Granulopoiesis and release of neutrophils into the peripheral blood have been improved, as indicated by the high levels attained at times. It would appear reasonable to conclude that, in this patient, the spleen exerted a constant inhibitory influence, probably hormonal in nature, and that removal of this action has improved the bone marrow's ability to recover from the depressed periods.

Summary

An unusual case is reported of cyclic agranulocytosis which developed following two isolated spontaneous attacks of acute agranulocytosis and which was characterized by a regular three week cycle and a progressively malignant course. Splenectomy resulted in improvement, without, however, altering the basic condition.

Addendum

The patient lived 16 months after splenectomy. Blood picture was essentially unchanged. She developed jaundice terminally and died after a massive gastric hemorrhage. At post mortem the pathological diagnosis was generalized lymphosarcomatosis involving viscera, lymph nodes and bones. Reëxamination of spleen and liver biopsy sections failed to show any changes which could be recognized as lymphosarcoma.

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THYROTOXICOSIS WITH FEATURES SIMULATING LYMPHOBLASTOMA *

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We have recently observed a patient with severe thyrotoxicosis and associated generalized lymphadenopathy. Following thyroidectomy, the lymphadenopathy disappeared. This case is reported because it deals with the interesting relationship between the thyroid, adrenal cortex and lymphatic systems.

Case Report

A 34 year old colored male entered Michael Reese Hospital on December 21, 1948. During the preceding year he had lost about 15 pounds of weight. One month before admission he began to vomit daily, usually after breakfast. One week later he developed a diarrhea, with five to six watery, loose stools a day. Two weeks before admission he complained of sharp pain in the right upper quadrant and mid-epigastrium. At the same time he noticed a generalized protrusion of his upper abdomen. This protrusion increased prior to his admission, and the pain became more intense. Throughout this period his appetite was good. There was no history of ankle edema, but slight exertional dyspnea was present prior to admission. Tremor of the right hand was noticed on occasions. No history of intolerance to heat was obtained. The past history was noncontributory.

Physical examination revealed a thin, 34 year old colored male, appearing acutely ill. His sclerae were slightly yellow. Moderate dyspnea but no orthopnea was present. The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic; pulse, 120 beats per minute. The temperature remained normal throughout the patient's hospital stay. The superficial cervical veins on the right side were more distended than on the left. A slight generalized enlargement of the thyroid gland was present. The left cardiac border was at the anterior axillary line. There was a pronounced apical thrust. Upper sternal dullness was present. The heart rate was about 120 beats per minute at the apex, with a pulse deficit of 30. The rhythm was totally irregular. No murmurs were audible. The lung fields were clear to percussion and auscultation.

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From the Department of Internal Medicine, Michael Reese Hospital, Chicago, Illinois.

The liver, markedly enlarged and tender, extended down to the level of the umbilicus, and the anterior surface actually bulged outward, so that a portion of the contour could be seen by the observer. The spleen was not palpable.

Scattered cervical lymph nodes, about 2 by 2 by 2 cm., were present bilaterally. Axillary nodes, about 3 by 2 by 2 cm., were also present bilaterally. These were hard, round, discrete and tender. A similar node was found in the right epitrochlear region. Several nodes were present in the left inguinal region. These were somewhat fixed and matted together.

No ankle, leg or sacral edema was present.

The marked lymphadenopathy, very large liver, increased distention of the cervical veins on the right side, dullness over the sternum on percussion, and complete absence of any peripheral or sacral edema led to the initial impression of lymphoblastoma, with mediastinal involvement and probable spread to the pericardium and myocardium.

In the course of the patient's examination, the venous pressure was found to be 330 mm. of water. This rose to 430 mm. of water when pressure was exerted over the liver. The circulation time (arm to tongue with Decholin) was 35 seconds; arm to lung with ether was 13 seconds. It was then apparent that the liver was enlarged as a result of congestion rather than of an infiltrative process. The auricular fibrillation and tachycardia, suggestion of enlargement of the thyroid and restlessness of the patient, together with the history of loss of weight, now indicated a diagnosis of primary hyperthyroidism with cardiac involvement and congestive failure. Subsequent laboratory data supported this diagnosis. The basal metabolic rate on December 29 was plus 37, and on December 31 was plus 44. The urine creatinine excretion was 228 and 627 mg./24 hours on two occasions. Other data were as follows: red blood cells, 4,530,000; hemoglobin, 89 per cent; white blood cells, 10,050, with 67 per cent segmented polymorphonuclear leukocytes, 6 per cent nonsegmented polymorphonuclear leukocytes and 27 per cent lymphocytes; sedimentation rate, 6 mm.; serum bilirubin, 4 mg. per cent; serum cholesterol, 120 mg. per cent, with 65 per cent esters; thymol turbidity, 4.2 units; thymol flocculation, three plus; cephalin-cholesterol flocculation, three plus; negative test for heterophile antibody. Biopsy of an axillary lymph node showed benign follicular hyperplasia.

The patient received Mercuhydrin and digitoxin, and a marked amelioration of the signs and symptoms of congestive failure followed. After receiving Lugol's solution for 17 days, the basal metabolic rate fell to plus 23 and the apical rate slowed to average 88 beats per minute. Twenty-three days after starting Lugol's solution, the patient underwent a subtotal thyroidectomy. He made an uneventful recovery and was discharged 18 days later in excellent condition. His cardiac rhythm spontaneously changed to a normal sinus mechanism.

The size of the lymph nodes decreased during the latter part of his hospital convalescence. Examination a few weeks following his discharge failed to reveal any residual lymphadenopathy.

Discussion

Numerous observers have noted a relationship between the thyroid gland and the lymphatic system. In 1908, Thomas Kocher [1] stated that the thyroid gland stimulated the lymphocyte-producing organs. In 1934, Dameshek [2] and his associates reported improvement in a patient with chronic lymphatic leukemia following total thyroidectomy. The lymph nodes and spleen regressed about 90 per cent from their original size after this procedure. Friedgood [3] reported a transient reduction in the size of the cervical lymph nodes in two patients with chronic lymphatic leukemia who received Lugol's solution. He also reported a remarkable decrease in the size of the spleen in two patients with idiopathic

splenomegaly following the administration of Lugol's solution. This occurred in a third patient with chronic myelogenous leukemia. McCullogh and Dunlap [5] reported the occurrence of a relative lymphocytosis in a large series of cases of hyperthyroidism.

Even though the relationship between the thyroid gland and the lymphatic organs has been recognized for a long period of time, the mechanism of this relationship is not yet understood. In 1926, Marine and Boas [6] suggested that the hyperplasia of the lymphoid tissue, so frequently found in hyperthyroidism, might be compensatory and secondary to injury of the suprarenal cortex and gonads by the hyperthyroid state. More recently, White and Dougherty [7] demonstrated dissolution of lymphoid tissue concomitant with lymphopenia, and an increase in the serum proteins following injection of adrenocorticotropic hormone or adrenal cortical hormone. In addition, Chase, White and Dougherty [8] showed that, concomitant with the fragmentation of the lymphocytes following adrenal cortical activity, antibodies were released and an augmentation of serum antibody titer occurred.

It is possible that the marked degree of hyperthyroidism present in our patient may have led to a state of adrenal cortical exhaustion, with resulting lymphadenopathy.

It is clear that the syndrome of thyrotoxicosis associated with generalized lymphadenopathy requires careful analysis of the functional status of the adrenal cortex. Such studies are necessary to establish the validity of the above chain of pathophysiologic events.

Summary

A thyrotoxic patient is reported with hepatomegaly and generalized lymphadenopathy so marked that the initial impression was lymphoblastoma. Following thyroidectomy, the lymphadenopathy disappeared within a short period of time. A possible etiologic mechanism is discussed in the light of studies concerning the relation between the lymphatic system and the endocrine system.

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HENOCH-SCHÖNLEIN'S SYNDROME WITH GLOMERULONEPHRITIS *

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SINCE Willan's [1] original description in 1808, the syndrome of purpura, edema or erythema associated with visceral symptoms and signs has evoked sporadic interest among clinicians. Schönlein [2] described purpura associated with arthritis in 1837. Some 30 years later Henoch [3, 4] noted gastrointestinal disturbances associated with this skin phenomenon. Sir William Osler was intensely interested in this subject, and between 1895 and 1914 wrote numerous papers on the variability of the skin lesions,[5, 6] the variety of the visceral lesions,[7, 8] and the importance of these visceral symptoms and signs from a surgical standpoint.[9] Pratt [10] subsequently reviewed both his own and Osler's experiences with this syndrome.

Henoch-Schönlein's syndrome occurs in both children and adults. From a study of the cases reported in the literature, it would seem that it is more frequently encountered in pediatric practice, and that neither sex is immune. In the uncomplicated case the prognosis is good, since there is usually complete recovery from the immediate episode, although there is a great tendency to recurrences at intervals varying from weeks to years. However, during the recurrences both the skin lesions and the visceral manifestations may present wide variations from the initial attack. Pathologically there is an increased capillary permeability, with either exudation of blood producing purpura and hemorrhage in various organs, or of plasma producing urticaria or edema of the involved viscera. The resemblance to serum sickness is marked. The etiology is thought to be on an allergic basis. In his earliest papers, Osler noted the resemblance of some of the symptoms of Henoch-Schönlein's syndrome to symptoms in his patients who were allergic to various foods. However, he did not attempt to isolate the specific allergenic agents. Duke [11] first reported specific hypersensitivity to food as a cause for Henoch-Schönlein's syndrome in 1921. Alexander and Eyerman [12] noted the complete syndrome in a patient who was allergic to milk; they reproduced the clinical picture by giving milk to the patient. Since the reports of Duke and Alexander and Eyerman, numerous foods and drugs have been implicated as etiologic agents. However, as in other allergic diseases, a specific causative agent cannot always be discovered. In passing, it must be remembered that one may develop a true thrombocytopenic purpura as an allergic phenomenon.[13]

Laboratory Findings: The platelets in the peripheral blood are within normal limits, as are the megakaryocytes in the bone marrow. The level of the red blood cells and hemoglobin is dependent upon the amount of blood lost in hemorrhage. Mild leukocytosis with polynucleosis is occasionally found at the onset. Bleeding, coagulation, prothrombin and clot retraction times are normal. The urea nitrogen may be elevated when there is bleeding into the gastrointestinal tract or when there are renal complications. The urine may show either microscopic or

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gross hematuria. Albuminuria and casts appear when there is a complicating glomerulonephritis. Bleeding into the central nervous system may produce red blood cells in the spinal fluid.[14] The capillary fragility test was found to be positive in 25 per cent of a large series of cases.[15] Occasionally there is an eosinophilia in the peripheral blood or bone marrow.

The skin lesions are variable and may occur in many combinations. They either precede or follow the appearance of the visceral manifestations. When skin lesions appear first, problems in diagnosis are minimized. There may be localized edema (particularly over the dorsum of the hands), urticaria, angioneurotic edema, erythema, petechiae, purpura (which may be confined to the extensor surfaces of the legs), and hemorrhagic bullae, with subsequent necrosis and/or painless ecchymoses. When purpura is absent and visceral lesions are present at the onset, a detailed past history may make the diagnosis less obscure.

Arthritis may be the first symptom of the disease and may even be migratory. The knees and ankles are most commonly affected. The joints appear swollen, are painful upon movement and are tender to touch. The arthritis leaves no residua.

Gastrointestinal symptoms are most frequent and are ushered in by nausea and by localized or diffuse colicky pains. Spasm of the smooth muscle of the digestive tract has been demonstrated radiologically. Christian [16] noted pylorospasm on roentgen-ray during an exacerbation in one of his cases in 1917. Alexander and Eyerman [17] also noted spasm in some part of the gastrointestinal tract on roentgen-ray study. Whitemore and Peterson [17] described irregularity of the terminal portion of the duodenum, with dilatation of the first portion of the jejunum. Kraemer [18] confirmed the latter findings. There may be hematemesis, tarry or frankly bloody stools, and abdominal distention of varying degree. In addition to spasm, infiltration of the abdominal viscera with blood and serum also produces pain. Frequently there are hemorrhages into the serosa, particularly of the small bowel. The abdominal muscles may be spastic or truly rigid, either locally or diffusely. These findings, particularly when skin lesions have not yet appeared, are in many instances suggestive of acute appendicitis, intestinal obstruction, ileitis, intussusception and intestinal perforation secondary to necrosis. The latter two conditions are indications for emergency surgery. Osler [9] and, more recently, Althausen, Deamer and Kerr [19] have stressed the importance of accurate diagnosis in differentiation of the "false" from the true acute abdomen in order to save patients from unnecessary laparotomies.

The *central nervous system* may be involved, with delirium, transient or permanent aphasias, hemiplegias and meningitis.

Renal bleeding, with clot formation in the ureters, may account for a classic clinical picture of ureteral colic. There is frequent microscopic or gross hematuria. Johnson [20] stated in 1852 that "disease of the kidney, with albuminous urine, is very common in connection with purpura." Osler [7, 8] described an acute hemorrhagic nephritis with albuminuria, casts and red blood cells as distinct from the hematuria associated with bleeding into the skin and mucous membranes. He noted that nephritis developed either at the height of the skin lesions or weeks later. Seven of Osler's patients died in uremia. In a paper entitled "A Fatal Case of Schönlein's Disease," with necropsy performed by MacCallum, Watson [21] reported autopsy findings of classic glomerulonephritis. However, the clinical

diagnosis of Henoch-Schönlein's syndrome was not convincing. Lippmann [22] reported six cases of "hemorrhagic" purpura associated with glomerulonephritis. Pratt [10] concurred with Osler on the occurrence of true glomerulonephritis as one of the most serious complications of Henoch-Schönlein's syndrome. Christian,[16] on the other hand, believed that the kidney lesions were due to the same process as that occurring in the skin. While many textbooks of medicine, hematology, dermatology and systems of medicine refer to true glomerulonephritis as a complication of this syndrome, one finds that they refer to Osler's original reports and have no further evidence. Standard textbooks of pathology make no reference to the association of glomerulonephritis with Henoch-Schönlein's syndrome. Moore,[23] after an extensive search in the recent literature, could find no pathologic descriptions of kidneys from patients who had died of glomerulonephritis in association with Henoch-Schönlein's syndrome. Consequently case 2 assumes great importance, since the kidneys at necropsy revealed a typical glomerulonephritis. In view of the fact that there was no evidence of renal disease antedating the terminal illness, one must consider the possibility that true glomerulonephritis may complicate Henoch-Schönlein's syndrome. On the other hand, as pointed out by Oliver,[24] there is no reason why both diseases may not have occurred simultaneously in the same patient.

Case Reports

Case 1. The patient was a 50 year old white male who was admitted to the Veterans' Hospital, Manhattan Beach, Brooklyn, New York, in August, 1949. His chief complaints were vomiting and abdominal pain. The present illness had started in the last week of July with a generalized dermatitis due to poison ivy. The rash persisted during the first two weeks of August. On August 10 he received the last of a series of six injections of "Ivyol." Approximately one week later, all joints began to pain and swell. This was soon followed by persistent vomiting, abdominal cramps and a bloody diarrhea. The latter soon became tarry. He then became constipated, requiring enemata or cathartics. Ten days before admission a "pink rash" appeared on both feet, followed in 24 hours by generalized urticaria, pruritus and fever. A few days later, bright red spots were noted on the lower extremities. He received parenteral glucose and "allergy" pills. He also had received sulfonamides and penicillin after the rash appeared.

His past history revealed that he had had hives in 1945 following sulfa medication. Otherwise he had never been seriously ill. Military induction examination in 1942 and discharge examination in 1946 did not reveal any hypertension, albuminuria or hematuria. Previous insurance examinations were also negative for cardiovascular-renal disease. His mother had died at the age of 68 of a cerebral hemorrhage. The family history was otherwise noncontributory. Review of his systems was negative.

Admission examination revealed a well nourished and well developed middle aged white male in no acute distress. His temperature was normal, pulse 106 and blood pressure 172 mm. Hg systolic and 108 mm. diastolic. There was no adenopathy. The conjunctivae were somewhat pallid. Examination of the lungs, heart and abdomen was not remarkable. Numerous petechiae were scattered over the lower portion of both legs. Many brownish macules, thought to be fading purpuric areas, were noted over the lower extremities. The remainder of the examination was within normal limits.

Laboratory Data: The red blood count was 3.84 million, with a hemoglobin of 11.4 gm. The white blood count was 9,450, with 84 per cent neutrophils, 2 per cent stabs and 14 per cent lymphocytes. The platelet count was 550,000. The sedimentation rate was 25 mm. in one hour. Bleeding, clot retraction, coagulation and prothrombin times were normal. Blood serology was negative. The blood urea nitrogen was 21.4 mg. per cent. Urea clearance and phenolsulfonphthalein kidney function

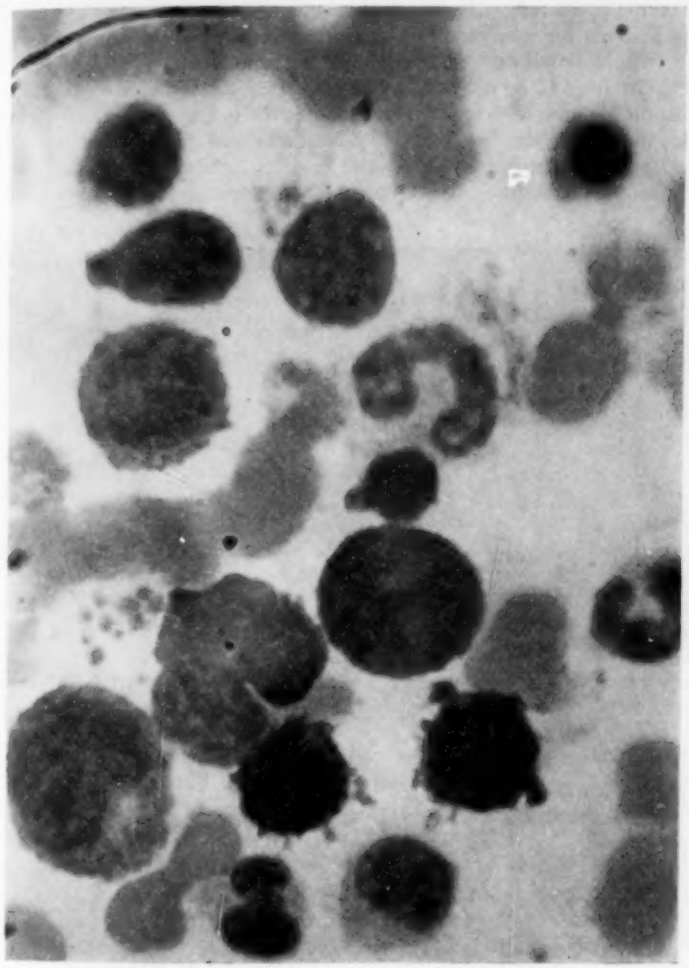

FIG. 1. *Case 1,* normal bone marrow with eosinophilia.

tests were normal. Urine examination revealed good concentration, a trace of albumin, and three to seven red blood cells per high power field. Three plus occult blood was found in the stools. Sternal marrow aspiration revealed normoblastic hyperplasia with an increase in eosinophils (figure 1).

On bed rest, antihistamines, calcium gluconate and ascorbic acid therapy, the patient made an uneventful recovery from his presenting illness. His blood pressure

dropped to 140/96. However, a few red blood cells persisted in the urine up to the time of discharge.

Case 2. The patient was a 58 year old white male who was admitted to Triboro Hospital, Queens, New York, in March, 1947, with bilateral pulmonary tuberculosis. He was treated conservatively throughout his hospitalization. History and repeated routine urine and blood chemistry examinations revealed no evidence of renal disease. The history was negative for allergic manifestations. His course was uneventful until June 9, 1949, when he developed an acute sinusitis and pharyngitis. A throat culture was positive for nonhemolytic streptococcus and *Staphylococcus aureus.* On June 15 he was injected with 300,000 units of penicillin in beeswax and oil intramuscularly. On June 17 he developed a papular rash on his hands and face. He was treated with antihistaminic drugs. The patient slowly improved until June 25, when he developed purpuric spots on the cheeks, buttocks and all extremities. On June 27 he developed gross hematuria and pain and swelling of the elbows, wrists, ankles and metacarpal-phalangeal joints. The pharyngeal mucosa was hemorrhagic. On this

FIG. 2. *Case 2,* distended ankle joint, necrotic residua of hemorrhagic bullae and purpura.

date the white blood count was 31,800, with 91 per cent neutrophils and 9 per cent lymphocytes, hemoglobin 14 gm., sedimentation rate 23 mm. in one hour, platelets 280,000, prothrombin time 89 per cent of normal; the fragility of the red cells and bleeding and clotting times were normal. Bone marrow aspiration revealed mild normoblastic hyperplasia; the megakaryocytes were normal. Throughout this period the patient did not appear to be severely ill.

On July 2 his condition suddenly became critical. His abdomen became greatly distended and he vomited large quantities of reddish-brown fluid. Gross hematuria persisted. The purpuric lesions became larger and so distended with blood that great hemorrhagic bullae were formed. The joint swellings became massive. The ileus was treated with Wangensteen suction and parenteral fluids. Large doses of vitamin K, ascorbic acid and antihistaminic drugs were administered. In spite of intensive therapy, the downward course persisted and exsanguination became so prominent a feature that daily transfusions were required. Nitrogen retention was also an outstanding feature at this time. After July 15 the symptoms and signs

began to abate so that the patient seemed well on the road to recovery. The hematemesis, melena and gross hematuria disappeared and the purpuric and bullous skin lesions showed steady resolution (figure 2). When the gross hematuria disappeared, albuminuria and microscopic hematuria were persistent findings.

On July 22 the temperature rose suddenly to 101° F., the pulse to 130, and respirations to 32. Examination disclosed diffuse subcrepitant râles throughout both lung fields. This was interpreted as an acute caseating bronchopneumonia. In spite of intensive therapy, the patient died on July 23.

	June 17	July							
		13	14	15	18	19	20	21	22
Transfusions			500 c.c.		500 c.c.	500 c.c.	500 c.c.	500 c.c.	500 c.c.
Hgb. (gm.)	14	10	9	11	5.5	6	7	10.5	
RBC (million)	4.8	3.7	3.3	3.77	1.73	2.68	2.89	4	
WBC (thousand)	31	22		37	21	18	9		
Plat. (thousand)	280			220					
BUN (mg.%)		88		100				85	80
Creat. (mg.%)		2.4						7	

Necropsy was performed five hours after exitus. The cause of death was found to be extensive caseating tuberculous bronchopneumonia throughout both lower lung fields. Grossly, the *gastrointestinal tract* was normal except for the proximal end of the jejunum, where there was a 5 cm. area of raised, firm lesions with slightly ulcerated bases, each of which measured approximately 0.5 cm. in diameter and was irregularly placed around the mucosa. The lesions were soft and friable and tended to be pedunculated. No other bleeding points were found. The *kidneys* were slightly enlarged but normal in position. The cut section showed a well-demarcated cortex and medulla, with the cortex averaging 8 to 10 mm. in width. The capsule stripped with a slight amount of difficulty and the external surface was slightly granular. There were no scars. Both pelves were clear. There were no hemorrhages. The ureters appeared normal. The *bone marrow* was normal. The *skin* over the buttocks, lower extremities, upper extremities, abdomen and part of the neck had numerous eschars, measuring 1 to 4 cm. in diameter and with irregular outlines. In some places over the abdomen, petechial-like subcutaneous hemorrhages were seen. There was no inflammation around the lesions. No bullae were present. None of these lesions appeared recent.

Microscopic examination of the *kidneys* (figures 3 and 4): The capsule was straight and thin. A small, subcapsular, web-shaped arteriosclerotic scar was present. There was no diffuse increase in interstitial fibrous tissue. The proximal convoluted tubules showed severe swelling, degeneration, vacuolation of the cells and dilatation of the lumen. Some hyalin cast formation and many areas of fresh red blood cells were present in the tubular lumina. The collecting tubules were empty. The glomerular tufts showed increased cellularity. There was a definite reduplication of Bowman's capsule, with crescent formation and fusion to the tufts. No collections of polynuclears were seen near the glomerulae. *Microscopic section of skin* of a purpuric area: There was normal squamous epithelium except over one small section,

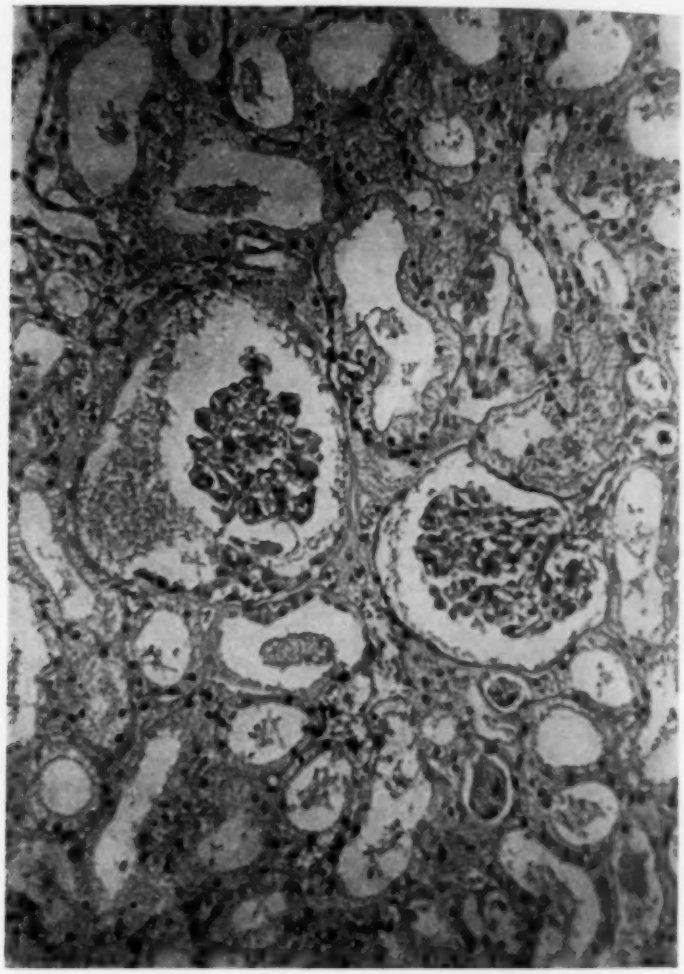

FIG. 3. *Case 2*, microscopic section of kidney (low power) revealing glomerulonephritis.

where flattening, thinning and loss of papillae occurred. In the corium there were collections of fresh red cells which appeared to fill dilated lumina of endothelial-lined channels. Numerous red cells were found extraluminally in the fibrous connective tissue.

SUMMARY

1. The literature on Henoch-Schönlein's syndrome with special reference to associated glomerulonephritis has been reviewed.

2. The present paper describes two cases of Henoch-Schönlein's syndrome with associated glomerulonephritis. In the first case, the diagnosis of glomerulonephritis is based on clinical evidence and the case must be assumed to be a recent acute episode, since previous examinations up to relatively recent time failed to reveal any evidence of glomerulonephritis. In the second case, repeated urine

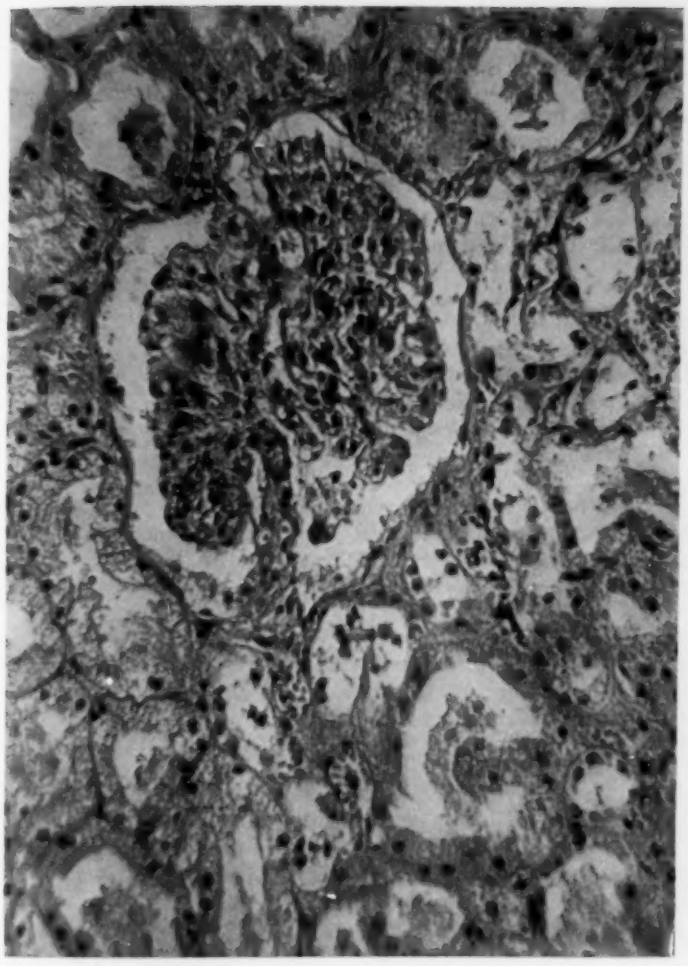

FIG. 4. *Case 2*, microscopic section of kidney (high power) revealing reduplication of Bowman's capsule, adhesions, exudation, swelling and tufting.

and blood examinations throughout a hospital stay of two years were within normal limits. The patient was apparently recovering from his episode of Henoch-Schönlein's syndrome when he succumbed to an extension of his tuberculosis. Necropsy findings revealed a subacute glomerulonephritis.

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EDITORIAL

RECENT STUDIES ON THE TREATMENT OF MOTION SICKNESS

An increasing proportion of the world's population is subjecting itself to a variety of motions in every day life—in ships, trains, cars, elevators, airplanes and "amusement" devices. As an indication of the vast numbers who expose themselves, it may be mentioned that no less than 25 million passengers were carried by the airlines of the world in 1949 (the figure for 1950 does not appear to be yet available).

The great significance of this rapid increase in the number of moving vehicles and the hordes who avail themselves of these conveniences, is that more and more individuals are being introduced to the unpleasant effects of motion. A safe, inexpensive and effective remedy for "motion sickness" is therefore a goal well worth achieving, and one which will inevitably earn the plaudits of the nauseated millions.

A notable step towards this achievement was made when "operation seasickness" was planned and executed in 1948. Gay and Carliner derived their original lead from a clinic patient at the Johns Hopkins Hospital who had been relieved of her carsickness as well as her hives by one of the newest antihistaminic compounds produced by G. D. Searle and Company and at that time known as "1694." Subsequently they offered the drug to a number of their friends and acquaintances who suffered from motion sickness of one sort or another, and results were almost uniformly good. Fortified with this limited but striking experience they persuaded the Chief of Staff and the Surgeon General of the U. S. Army to allow them to undertake an experiment with Dramamine (as the drug was later named) on a trans-Atlantic troopship. The "General Ballou" was ideal for this purpose, being narrow and built high out of the water—perfectly designed for the facile production of seasickness. And so on November 27, 1948, along with some 1,300 troops, these hardy physicians embarked.

The voyage apparently fulfilled every hope and expectation and, as ubiquitous vomiting got into full swing, conditions on the ship became indescribably repulsive. The investigators conducted an experiment which is well known, and it is unnecessary to give more than an outline of their results.[1, 2] In brief they claimed that 372 out of 389 (over 95 per cent) seasick men derived complete relief from Dramamine within one hour. In a prophylactic study they found that only 2 out of 134 men developed any symptom of seasickness (dizziness only) while on the drug, while of a collateral group of 123 men receiving a placebo 35 became nauseated or vomited. They concluded that Dramamine was "more uniformly effective in the

[1] Gay, L. N., and Carliner, P. E.: The prevention and treatment of motion sickness. I. Seasickness, Bull. Johns Hopkins Hosp. **84**: 470, 1949.

[2] Gay, L. N., and Carliner, P. E.: The prevention and treatment of motion sickness. I. Seasickness, Science **109**: 359, 1949.

prophylaxis and treatment of motion sickness than any drug so far employed."

These results were indeed striking. But the methods of the experiment have been criticized by Tyler and Bard [3, 4] who pointed out, first, that the method of dividing the subjects into control and medication groups on the basis of the ship's compartments was experimentally hazardous, as different compartments are not subject to the same kind and degree of motion; and, as a matter of fact, the two compartments used were not on the same deck. Moreover there are other ways in which one compartment may be more conducive to the development of seasickness than another. To have ensured proper control the investigators should have randomly divided the men in each compartment into the various experimental groups. In evidence that such a criticism is valid these critics point to the incidence of seasickness in two other compartments of the ship which bore the same spatial relationship to each other as the two used in the experiments. In these other compartments the incidence of seasickness was three times as great in one (33 per cent) as in the other (11.6 per cent), thus showing that the difference between incidence in the treated and untreated groups could not safely be attributed to the medication alone.

Secondly, they point out that to evaluate the prophylactic efficacy of a drug it must be tested under conditions in which the incidence of sickness is high. The sickness rate in the "General Ballou" experiment was not high (20 to 30 per cent), and at low rates many drugs give excellent protection, such as thiobarbiturate. At higher rates of sickness (50 per cent or more) the effectiveness of many of these preparations falls off and may be completely lost. Furthermore, as the drug was not directly compared with hyoscine or any other effective remedy already available, it was clearly premature to hail Dramamine as the most effective prophylactic so far employed.

Thirdly, although the report concerning the cure of severely seasick men was impressive, even here there were two uncontrolled factors which may have influenced the results. Controls did not continue to receive placebos or remain untreated during the observation periods of those who received the drug; many of the controls who became sick were then given Dramamine and placebos alternately. This therefore made it quite impossible to determine with any exactitude the extent to which changes in the ship's movements contributed to remission of symptoms. In the same way it was impossible to know what influence the important phenomenon of adaptation had on the symptoms—an influence which may be of great significance in any prolonged exposure to motion.

Despite these cogent criticisms it was clear that Dramamine achieved many rapid and complete cures of severe seasickness. The actual supremacy of the drug over all others, however, remained unproven as no direct com-

[3] Tyler, D. B., and Bard, P.: Motion sickness, Physiol. Rev. **29**: 311, 1949.
[4] Tyler, D. B.: Dramamine and motion sickness, Science **110**: 170, 1949.

parisons were made. It may be mentioned, as has been pointed out by Nickerson,[5] that although early reports gave the impression that Dramamine was a new drug it was really no such thing. It was merely the combination of two well known compounds, Benadryl and a simple derivative of theophylline.* Apparently the methyl xanthine compound was chosen in an attempt to offset the drowsiness so often caused by the antihistamine,[6] although there is neither pharmacological nor clinical evidence that the quantity of the methyl xanthine incorporated in each dose of the "new" drug should have any noticeable effect.[5]

In a carefully controlled study Chinn and Oberst [7] used the "simulated turbulence" technic of Strickland and Hahn [8] to compare the effectiveness of placebos, Benadryl, 8-chlorotheophylline, Dramamine, hyoscine and a hyoscine-Benadryl mixture in the prevention of airsickness. Strickland and Hahn had found that in controlled artificially turbulent conditions 55.6 per cent of 108 men receiving the placebo vomited, while only 28.7 per cent of 108 who received Dramamine vomited. In other words Dramamine afforded definite protection against motion sickness even where high incidence rates were involved. It did in fact protect approximately 48 per cent of the candidates from the evils of airsickness.

The results obtained by Chinn and Oberst afford an interesting extension of this work. Of their placebo groups 53.3 and 66.6 per cent vomited, while the percentages of those who vomited when premedicated with one of the drugs investigated were as follows: 8-chlorotheophylline, 50 per cent; Benadryl 30.7 per cent; hyoscine 19.3 per cent; hyoscine-Benadryl 10.3 per cent. In other words no significant difference was observed between Benadryl and Dramamine; and better than either of them was hyoscine; while best of all was the combination of Benadryl and hyoscine. Strickland, Hahn and Adler [9] later adduced evidence which strongly suggested that Dramamine was no more effective than a placebo in preventing swing sickness in susceptible subjects, while it had previously been shown [10] that hyoscine was highly efficacious.

It may further be pointed out that the efficacy of hyoscine in prophylaxis of motion sickness had been repeatedly demonstrated earlier. Holling, McArdle and Trotter [11] found that on short sea trips 42.5 per cent of 212 men on dummy tablets vomited, while only 14 per cent of 218 who received

[5] Nickerson, M.: Dramamine, Science **111**: 312, 1950.

* Benadryl is diphenhydramine hydrochloride, and Dramamine is the 8-chlorotheophylline salt of diphenhydramine.

[6] Cusic, J. W.: Note on the chemistry of Dramamine, Science **109**: 575, 1949.

[7] Chinn, H. I., and Oberst, F. W.: Effectiveness of various drugs in prevention of airsickness, Proc. Soc. Exper. Biol. and Med. **73**: 218, 1950.

[8] Strickland, B. A., and Hahn, G. L.: The effectiveness of Dramamine in the prevention of airsickness, Science **109**: 359, 1949.

[9] Strickland, B. A., Hahn, G. L., and Adler, H.: Studies on airsickness, J. Aviation Med. **21**: 90, 1950.

[10] Smith, P. K., and Hemingway, A.: Effect of hyoscine on swing sickness and on performance. USAF School of Aviation, Med. Res. Proj. Report No. 1: 11, 1946.

[11] Holling, H. E., McArdle, B., and Trotter, W. R.: Prevention of seasickness by drugs. Lancet **1**: 127, 1944.

hyoscine vomited. Similarly Tyler [12] had shown, with sickness rates as high as 53 per cent in the placebo group, that hyoscine alone or a combination of hyoscine with amytal and atropine * gave protection to an appreciable percentage of those receiving it—for only 27 per cent of those thus treated became sick. Lilienthal [13] had also shown hyoscine to be highly effective in prophylaxis though at much lower sickness rates. It has been demonstrated by the advocates of Dramamine that it can be given every few hours round the clock for many days without significant side effects. This is undoubtedly true. But it has been added as a corollary that no one would think of repeating the dose of hyoscine in this way. This contention ignores the fact that at least one group of observers [11] has actually employed this technic, giving hyoscine 0.6 mg. as a starting dose, followed by 0.3 mg. every six hours for 48 hours without significant side effects.

Many subsequent experiments have been made to test the prophylactic efficacy of Dramamine. Chinn and his coworkers [14] have recently looked into the matter at sea. As well as Dramamine these investigators employed Benadryl, hyoscine, and Artane, and also some other antihistamines—Perazil, Thephorin and Neo-antergan. They found that Benadryl, Dramamine and hyoscine were all effective in preventing seasickness, but they preferred Benadryl or Dramamine because these drugs produced side effects in a smaller number of cases. Artane was also notably effective, but the remaining antihistamines were of little or no value. The number in each series treated was not large, and so strictly comparative results are not available.

Wright [15] reports his results in the prophylaxis of seasickness in 1,600 persons. These passengers were treated alternately with placebo, M.S.P., Dramamine, and Benadryl. Of those receiving no medication 32.1 per cent had symptoms of seasickness; with placebos 27 per cent were affected; with M.S.P. 17.8 per cent became seasick; with Benadryl 9.7 per cent; and with Dramamine 8.1 per cent.

As the prophylactic position now stands it seems clear that no final answer has been given. Hyoscine, Benadryl and Dramamine, judging by the weight of evidence so far accumulated, are all markedly effective. The work of Chinn and Oberst [7] would appear to provide evidence that the best medication of all will prove to be a combination of hyoscine with Benadryl (or perhaps with Dramamine).

In the active treatment of established motion sickness it appears that Dramamine holds almost undisputed pride of place, though Chinn and his colleagues [14] found in a small number of patients that both hyoscine and Dramamine showed only "a suggestive but insignificant superiority to

[12] Tyler, D. B.: The influence of a placebo, body position, and medication on motion sickness, Am. J. Physiol. **146**: 458, 1946.

* M.S.P.—Army Motion Sickness Preventive.

[13] Lilienthal, J. L.: The effect of hyoscine on airsickness, J. Aviation Med. **16**: 59, 1945.

[14] Chinn, H. I., Noell, W. K., and Smith, P. K.: Prophylaxis of motion sickness: evaluation of some drugs in seasickness, Arch. Int. Med. **86**: 810, 1950.

placebos." Wright,[15] however, in his much larger series involving 1,200 seasick passengers, found that whereas M.S.P. had "cured" about 50 per cent by the end of two hours, Benadryl and Dramamine had "cured" 88 and 91 per cent respectively.

A number of other investigations with Dramamine have been carried out —too numerous for analysis here. Many of these are unconvincing, being poorly or not at all controlled, involving too few subjects and at too low sickness rates for valid conclusions to be drawn, and often merely representing the impressions of the individual investigators. Nowhere, however, is Dramamine's place as the most effective available remedy for established seasickness seriously challenged.

The usefulness of Dramamine is not limited to the control and prevention of motion sickness alone. A number of reports have recently appeared which give promise that Dramamine may prove a merciful salvation in many conditions characterized by nausea and vomiting. A preliminary report on its effectiveness in the nausea and vomiting of pregnancy was made by Carliner, Radman and Gay.[16] They administered Dramamine to 43 women who had complained of nausea and vomiting for four to six weeks and who had failed to respond to pyridoxine, thiamine, sedation or psychotherapy. Of these patients 31 were completely relieved of their symptoms within three hours of the first dose.

This drug has also been claimed to relieve the distressful syndrome of radiation sickness,[17] to reduce the incidence of vomiting following the fenestration operation,[18] and following anesthesia for other surgical procedures.[19, 20] It is claimed to be of value in miscellaneous vestibular disturbances,[21] including Ménière's disease. And, as Shaw [22] suggests, since it is an antihistaminic it will no doubt have its fling in the treatment of the common cold.

Despite the fact that a number of the experiments with Dramamine have left much to be desired as controlled scientific studies, there is no reasonable room for doubt that the drug is of appreciable value in many conditions associated with vomiting. There is as yet no clear-cut and conclusive evidence, however, that it is superior to Benadryl in any condition, nor that it is superior to hyoscine in many of its applications to motion sickness. The question remains, how does Dramamine work? Much study has been under-

[15] Wright, W. L.: Effectiveness of newer drugs in seasickness, U. S. Armed Forces M. J. **1**: 570, 1950.

[16] Carliner, P. E., Radman, H. M., and Gay, L. N.: Treatment of nausea and vomiting of pregnancy with Dramamine—preliminary report, Science **110**: 215, 1949.

[17] Beeler, J. W., Tillisch, J. H., and Popp, W. C.: A new drug in the treatment of radiation sickness, Proc. Staff Meet. Mayo Clin. **24**: 477, 1949.

[18] Campbell, E. H.: The effectiveness of Dramamine in relieving the vestibular reactions following the labyrinthine fenestration operation, Laryngoscope **59**: 1261, 1949.

[19] Rudolph, C. J., Park, D. D., and Hamilton, C.: Treatment of post-anesthesia nausea and vomiting, J.A.M.A. **144**: 1283, 1950.

[20] Rubin, A., and Metz-Rubin, H.: The effect of Dramamine upon post-operative nausea and vomiting, Surg., Gynec. and Obst. **92**: 415, 1951.

[21] Gay, L. N.: Prophylactic and therapeutic control of vestibular disturbances with dimenhydrinate, J.A.M.A., **145**: 712, 1951.

[22] Shaw, C. C.: Dramamine trials in the United States Navy, Military Surg. **106**: 441, 1950.

taken to elucidate the mode of action of this compound, but as yet the secret has not been unlocked.

As the drug is an antihistamine it was thought that this might explain its action. But since it has been shown that several antihistamines have no influence on motion sickness,[14] this must be abandoned as the sole explanation of its activity. It was thought that possibly its sedative effect was the answer; but the relative ineffectiveness of stronger sedatives, and the demonstration that counteracting the sedative effect of Dramamine with the simultaneous administration of benzedrine did not interfere with its influence on motion sickness,[15] made this supposition untenable.

There is evidence that its action is a direct one on central connections of the vestibular apparatus. In 1949 Freedman and Himwich [23] showed that if di-isopropyl fluorophosphate (DFP) were injected into the carotid artery of rabbits, the animals developed a compulsion to pivot on their hind legs away from the side on which the injection had been made. These workers labelled this induced disturbance as the "adversive syndrome." Similar "forced circling" movements had previously been induced by various anatomic lesions in the central nervous system. Atropine, hyoscine, Benadryl and Dramamine have all been shown capable of correcting or preventing the circling movements of this adversive syndrome.[24] This syndrome also yields to two other antihistamine drugs, phenergan and lergigan, while Thephorin, Antistine, Pyribenzamine, Neo-antergan and Chlor-trimeton are ineffective.[25] It has recently been demonstrated that Dramamine raises the threshold of effective vestibular stimulation to the microcaloric test and to galvanic stimulation.[26] All of these findings are, of course, compatible with either a direct effect on the peripheral vestibular apparatus, or on a more central mechanism.

Evidence advanced in favor of the more central action is the fact that subconvulsive doses of DFP in animals produce grand mal-like EEG patterns, and these electrical changes can be neutralized by Dramamine.[27] Moreover it was shown by Schiff and his coworkers [24] that the local application of DFP to the inner ear in rabbits and cats did not induce the adversive syndrome as its intravenous injection did. This suggested that Dramamine, which controlled the intravenously induced syndrome, counteracted the anticholinesterase effect of DFP at a more central level. It is suggested by these investigators that such findings indicate a probable localization of the

[23] Freedman, A. M., and Himwich, H. E.: DFP: Site of injection and variation in response, Am. J. Physiol. **156**: 125, 1949.

[24] Schiff, M., Esmond, W. G., and Himwich, H. E.: Forced circling movements (adversive syndrome): correction with dimenhydrinate ("Dramamine"), Arch. Otolaryng. **51**: 672, 1950.

[25] Johns, R. J., and Himwich, H. E.: The central action of some antihistamines, Am. J. Psychiat. **10**: 367, 1950.

[26] Gutner, L. B., Gould, W. J., and Batterman, R. C.: Studies on pharmacology of Dramamine, Federation Proc. **9**: 280, 1950.

[27] Esmond, W. G., Johns, R. J., Bales, P. D., McCauley, A., and Himwich, H. E.: Convulsant and anticonvulsant effects of some antihistamines, Electroencephalog. Clin. Neurophysiol. **2**: 115, 1950.

effect of Dramamine "to subcortical cerebral areas associated with vestibular function." They compare the action of morphia, which probably does not affect pain receptors but alters the central interpretation of pain, and suggest that Dramamine, without affecting peripheral receptors, may alter central responses to vestibular stimuli.

Much still remains to be elucidated. First many of the clinical claims made for Dramamine must be substantiated. If in the field of experimental therapeutics these claims are vindicated, then it remains to explain how its effectiveness in such disturbances as hyperemesis gravidarum and radiation sickness can be correlated with an action on central stations associated with vestibular function. It seems likely that other sites of central action will have to be invoked.

It is noteworthy that almost all the experiments with Dramamine have involved young, presumably healthy males. There is no reason to suppose that results would prove significantly different in other groups, but it would be interesting to see valid statistical comparisons. Side effects, which have been uncommon and unimportant in most series, might well prove more troublesome in less hardy segments of the population.

Meanwhile the pioneer work of Gay and Carliner has done the valuable service, not only of introducing an effective agent in the control of motion sickness, but of focusing attention on the mechanism and therapy of this almost universal syndrome. There is no doubt that Dramamine has proved itself (or at any rate its Benadryl moiety) to be a great boon to millions in this era of travel. It would seem to be a fair estimate that, under rigorous conditions of controlled testing when the sickness rate is high, the drug will protect about half of those susceptible from the discomforts of motion sickness. Once sickness has developed it probably cures about the same proportion, though an appreciable simultaneous recovery rate (from adaptation or other factors) will make it appear that the drug has cured a much larger percentage.

Because of the enormous number of persons who have benefited and will benefit from the drug, it must take its place among the significant advances of the sensational forties. No era in medicine has given us such an impressive array of new remedies, and it is interesting to compare and contrast the credentials of our various developments. Some owe their prestige to their life-saving qualities, which may only be applicable to an insignificant number of sufferers; while others gain distinction only because of the multitudes to whom they render more modest assistance. Thus, for example, the Blalock-Taussig operation confers a maximum benefit, but only on a very limited few; while Dramamine has conferred and will confer a minor, though most welcome, benefit on countless millions.

H. J. L. M.

REVIEWS

Methods in Medical Research. Vol. 4. MAURICE B. VISSCHER, Editor-in-Chief. 306 pages; 14 × 22.5 cm. The Year Book Publishers, Inc., Chicago. 1951. Price, $7.00.

The summaries of methodology in this volume include histochemistry, water and electrolyte metabolism, gastrointestinal physiology and tissue culture. The section on histochemical staining methods is written by George Gomori and includes technics for inorganic and organic substances including enzymes. The section on fluid and electrolytes is edited by Louis B. Flexner and contains methods of measurement of total body water, plasma volume, extracellular fluid and calcium ion. An extensive discussion of the flame photometer is presented. The gastrointestinal section is edited by J. P. Quigley and includes studies of pressure in gastrointestinal lumina, preparation of experimental fistulae and studies of the secretions and their stimulants and inhibitors. The section on tissue culture methods edited by C. M. Pomerat contains methods of observation and also preparation and maintenance of tissue cultures. These methods of observation include use of radioactive tracers and phase microscopy.

Investigators in a wide variety of medical fields will find that this volume as its predecessors suggests new approaches to some of their problems.

G. G.

Die orale Strophanthin Behandlung. By BERTHOLD KERN. 382 pages; 16.5 × 25 cm. Ferdinand Enke Verlag, Stuttgart. 1951. Price, gehefter DM 18.–; gebunden DM 21.–.

When, in 1905, Fraenkel introduced intravenous therapy with strophanthin, he probably never thought that oral strophanthin, discredited and abandoned for valid reasons, would be revived in 1951.

On 382 pages, the benefits to be derived from strophanthin given orally are expounded. If the author has hoped to convince the skeptical reader by scientific argument and clinical examples, he has achieved exactly the opposite result. From the case histories presented, one gains the impression that many patients who have benefited subjectively from oral strophanthin ("Strophoral") did not suffer from any cardiovascular disorder at all but more likely from various forms and degrees of psychiatric disorders. It should be of interest to the psychiatrist that "Strophoral" proved beneficial to the insomnia and palpitations of an aging maiden. From another case, one can learn that a young champion wrestler afflicted with occasional sticking chest pain was able to partake in and win an all day wrestling championship meeting after only a few doses of "Strophoral." Diuretics and sodium poor diets seemed to have produced no results in the author's experience. Little of any value can be found on the 382 pages of the book. It cannot be recommended.

A. G.

Arzneitherapie der Herzkrankheiten. By HANS-JUERGEN OETTEL. 253 pages; 17.5 × 24.5 cm. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune and Stratton, Inc., New York. 1951. Price, Ganzleinen DM 27.–.

This book on medical therapeutics of cardiac diseases attempts to familiarize the clinician with the numerous advances in the pharmacology of drugs acting upon the myocardium. The variations of pharmacological actions of a very large number of cardiac glycosides are emphasized and discussed in great detail. Many of the recom-

mendations are sound and of practical importance. However, other recommendations seem to have a more insecure basis. For instance, it is difficult to evaluate on what basis desoxycorticosterone and acetylcholine should be found advantageous if given in conjunction with cardiac glycosides. For the former, inadequate experimental and clinical data are given to justify its recommendation. For the latter, the risk does not appear inconsiderable as one might judge from the effect of coincidentally combined application of digitalis glycosides and drugs of strongly cholinergic principles. A similar judgment might be maintained for insulin and the probably ineffectual cytochrome. The book contains a good general discussion of the individual advantages and disadvantages of the different cardiac glycosides including those not as yet clinically tried in this country. The discussion is often of interest although often not too clearly presented.

The clinical recommendations to the practitioner based upon the varying properties of the cardiac glycosides are too complicated to be followed with benefit. As a matter of fact, their differences are not so great as to require familiarity with all of them for the "differential" treatment of cardiac decompensation.

Smaller, individual chapters follow on quinidine, ergot derivatives, adrenergic drugs, oxygen, carbon dioxide, caffein, pitressin, nitrite, iodides and thyroid preparations, anti-thyroid principles, and lobelin. The discussion in these chapters follows along conventional lines.

The discussion of diuretics for the cardiac patient is inadequate. It almost appears as if the author resorts to them only in rare instances. This serious omission, furthermore, adds to the inadequacies of the book as a guide for the drug therapy of cardiac patients. Hypnotics, like morphine and its synthetic relatives, and many other drugs are not discussed at all.

No references are given nor is an index supplied.

It is difficult to visualize to whom this book is supposed to appeal. It certainly cannot be regarded as a guide for the practitioner and internist since its clinical recommendations are vague and often confusing. The cardiologist cannot be interested in it since many scientific statements are not supported by references. The reviewer regards the author's previous publication, "Chemie, Pharmakologie und Klinik der Herzglycoside," Ergeb. d. inn. Med. **63**: 418–594, 1943, as a superior digest of the subject. The English literature contains better discussions on cardiac therapy.

A. G.

The Early Diagnosis of the Acute Abdomen. 10th ed. By ZACHARY COPE. 270 pages; 14.5 × 22.5 cm. Oxford University Press, London, New York and Toronto. 1951. Price, $3.50.

This brief classic needs little or no introduction to the English-speaking medical world. It is a reissue of a deservedly popular synopsis of acute abdominal diagnosis and should be read at some time early in the career of all medical men.

For the benefit of those who are not yet acquainted with this work, the author first deals with the principles of diagnosis, and then discusses history taking and the physical examination. He then deals with specific conditions in turn—appendicitis, perforated peptic ulcers, acute pancreatitis, acute intestinal obstruction, intussusception, cancer of the large bowel, volvulus, strangulated hernia, ectopic gestation, cholecystitis, and the colics. The concluding chapters are devoted to the early diagnosis of abdominal injuries, the acute abdomen in the tropics, acute abdominal disease with genito-urinary symptoms, the diagnosis of acute peritonitis, and diseases which may simulate the acute abdomen.

Since the last edition in 1945 there have been few changes. A good radiogram illustrating large bowel obstruction has been added, and a number of brief paragraphs have been included on such subjects as the value of auscultation in the diagnosis of gunshot wounds of the intestine; the left-sided appendix; regional enteritis in the differential diagnosis of appendicitis; abdominal symptoms due to salt deficiency; and Bornholm disease simulating the acute abdomen. One is disappointed again to find no mention of a number of diseases, albeit rare, that can simulate acute abdominal disease, such as herpes zoster and acute porphyria; and it is a pity to find that the term "ptomaine poisoning" still receives the blessing of a scientific text.

Apart from such minor criticisms the book remains a valuable treatise on its subject, graphically written, well illustrated and nicely produced.

H. J. L. M.

From a Doctor's Heart. By EUGENE F. SNYDER, M.D., with a foreword by PAUL DUDLEY WHITE, M.D. 251 pages; 23.5 × 15.5 cm. 1951. Philosophical Library, New York. Price, $3.75.

This book was written by a physician during his recovery from myocardial infarction. It discusses heart disease, particularly coronary artery disease, in lay terms, and presents a sound philosophy for victims of this disease. It is interestingly written, containing autobiographical material, and describes the author's opinions on non-medical as well as medical problems of our times. It reflects a warm, thoughtful and mature personality.

S. S.

Eternal Eve: The History of Gynaecology and Obstetrics. By HARVEY GRAHAM. 699 pages; 15 × 23.5 cm. Doubleday and Company, Inc., Garden City, N. Y. 1951. Price, $10.00.

It is unfortunate that the identity of the distinguished British author-surgeon cannot be known generally so that the reader of this absorbing work could thank him personally. Harvey Graham is the pseudonym of the author. Beginning with the earliest myths through available records, the author guides the reader through the absorbing story of childbirth and gynecology to the present day in the most entertaining manner this reviewer has had the privilege of perusing. There is a brief bibliography, and an index of personal names and subjects. The book can be recommended most heartily to anyone who would read history in a diverting and yet enlightening form.

J. E. S.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Angiocardiography—Annals of Roentgenology, Volume XX. By CHARLES T. DOTTER, M.D., Assistant Professor of Radiology, Cornell University Medical College, etc.; and ISRAEL STEINBERG, M.D., Assistant Clinical Professor of Radiology and Medicine, Cornell University Medical College, etc. 304 pages; 27 × 20.5 cm. 1951. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $16.00.

Approved Laboratory Technic. 5th ed. By JOHN A. KOLMER, M.D., D.P.H., Sc.D., F.A.C.P., Professor of Medicine and Director of the Institute of Public Health and Preventive Medicine, Temple University, etc.; EARLE H. SPAULDING, Ph.D., Professor of Bacteriology, Temple University School of Medicine, and HOWARD W. ROBINSON, Ph.D., Professor of Physiological Chemistry, Temple University School of Medicine. 1,180 pages; 25.5 × 17 cm. 1951. Appleton-Century-Crofts, Inc., New York. Price, $12.00.

Atelektasen der Lunge die Verschiedenen Formen Ihre Entstehung und Bedeutung. By PROF. DR. MED. HANS ALEXANDER. 58 pages; 24 × 17 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 8.70.

Atlas of Framboesia: A Nomenclature and Clinical Study of the Skin Lesions. By KENNETH R. HILL, M.D., Professor of Pathology, University College of the West Indies, etc.; DR. R. KODIJAT, Director, Treponematoses Control Project in Indonesia, and DR. M. SARDADI, Research Team Leader. 52 pages; 24 × 16 cm. (paper-bound). 1951. World Health Organization, Geneva. Price, $1.00.

An Atlas of Normal Radiographic Anatomy. By ISADORE MESCHAN, M.A., M.D., Professor and Head of the Department of Radiology, University of Arkansas School of Medicine; with the assistance of R. M. F. FARRER-MESCHAN, M.B., B.S. (Melbourne, Australia). 593 pages; 26 × 17 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $15.00.

Autopsy Diagnosis and Technic. 3d ed. By OTTO SAPHIR, M.D., Pathologist, Michael Reese Hospital, etc. 471 pages; 19.5 × 13 cm. 1951. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, N. Y. Price, $6.00.

Body, Mind, and Sugar. By E. M. ABRAHAMSON, M.D., and A. W. PEZET. 206 pages; 21.5 × 14.5 cm. 1951. Henry Holt & Company, New York. Price, $2.95.

Cancer Cytology of the Uterus, Introducing a Concept of Cervical Cell Pathology. By J. ERNEST AYRE, M.D., Director, Dade County Cancer Institute, Cancer Cytology Center; and Chief, Cancer Research Department, Medical Research Foundation of Dade County, Miami, Florida, etc. 407 pages; 28 × 20 cm. 1951. Grune & Stratton, Inc., New York. Price, $14.50.

Diagnostische und therapeutische Technik beim Kinde. By DR. MED. KURT NITSCH. 168 pages; 21 × 15 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 14.70.

Diseases of the Nervous System. 4th ed. By W. RUSSELL BRAIN, D.M. (Oxon.), P.R.C.P. (London), Physician to the London Hospital and to the Maida Vale Hospital for Nervous Diseases, etc. 1,002 pages; 22.5 × 14.5 cm. 1951. Oxford University Press, New York. Price, $8.50.

Die generalisierten Tuberkulosen. By DR. MED. F. SCHMID. 230 pages; 24 × 17 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 24.–

Gynaecological Endocrinology for the Practitioner. 2nd ed. By P. M. F. BISHOP, D.M. (Oxon.), Senior Lecturer in Applied Physiology, Guy's Hospital Medical School, etc. 132 pages; 19 × 12.5 cm. 1951. The Williams and Wilkins Company, Baltimore. Price, $3.00.

Die hämolytischen Syndrome im Kindesalter. By PRIV. DOZ. DR. CONRAD GASSER. 322 pages; 25 × 17.5 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 45.–

The Healing Touch. By HARLEY WILLIAMS. 370 pages; 20.5 × 13.5 cm. 1951. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $6.75.

Internal Medicine: Its Theory and Practice. 5th ed. Originally edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Late Professor of Medicine in the Tulane University of Louisiana, School of Medicine, New Orleans, Louisiana; Fifth Edition edited by MICHAEL G. WOHL, M.D., F.A.C.P., Associate Professor of Medicine, Temple University School of Medicine, etc. 1,563 pages; 27 × 18.5 cm. 1951. Lea & Febiger, Philadelphia. Price, $15.00.

International Sanitary Regulations—World Health Organization Regulations No. 2, Adopted by the World Health Assembly 25 May 1951—World Health Organization Technical Report Series No. 41. 100 pages; 24 × 16 cm. (paper-bound). 1951. World Health Organization, Geneva. Price, 65 cents.

Management of Celiac Disease. By SIDNEY VALENTINE HAAS, M.D., Professor of Pediatrics and Director of the Department, New York Polyclinic Medical School and Hospital, etc.; and MERRILL PATTERSON HAAS, M.D. 188 pages; 24 × 16 cm. 1951. J. B. Lippincott Company, Philadelphia. Price, $5.00.

The Medical Annual: A Year Book of Treatment and Practitioners' Index—69th Year, 1951. Editors: SIR HENRY TIDY, K.B.E., M.A., M.D. (Oxon.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.SC., F.R.C.S. 509 pages; 22 × 14 cm. 1951. The Williams & Wilkins Company, Baltimore. Price, $7.00.

Die neuzeitlichen Brustwand- und Extremitäten-Ableitungen in der Praxis. By PROF. DR. HERBERT REINDELL and DR. HELMUTH KLEPZIG; with the assistance of PROF. DR. LUDWIG HEILMEYER. 179 pages; 25 × 17.5 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 22.50.

A Pediatric Manual for Mothers: Questions and Answers on the Care and Feeding of Infants and Children. By HARRY R. LITCHFIELD, M.D., Consultant in Pediatrics, Rockaway Beach Hospital, etc., and LEON H. DEMBO, M.D., Director of Pediatrics, St. Ann's Hospital, etc. 269 pages; 18.5 × 13 cm. 1951. Grune & Stratton, New York. Price, $2.50.

Peptic Ulcer: Clinical Aspects—Diagnosis—Management. Editor: DAVID J. SANDWEISS, M.D., F.A.C.P., Associate Attending Physician, Division of Internal Medicine, Harper Hospital, Detroit; Editorial Committee: A. H. AARON, HENRY L. BOCKUS, GEORGE E. DANIELS, GEORGE B. EUSTERMAN, L. KRAEER FERGUSON, A. C. IVY, SARA M. JORDAN, FRANK H. LAHEY, WALTER L. PALMER, HARRY SHAY, ALBERT M. SNELL, DWIGHT L. WILBUR. 790 pages; 25.5 × 16.5 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $15.00.

Pioneer Doctor. By LEWIS J. MOORMAN, M.D. 252 pages; 22 × 15 cm. 1951. University of Oklahoma Press, Norman, Oklahoma. Price, $3.75.

Psychosomatic Gynecology: Including Problems of Obstetrical Care. By WILLIAM S. KROGER, M.D., Assistant Clinical Professor of Obstetrics and Gynecology, Chicago Medical School, etc., and S. CHARLES FREED, M.D., Adjunct in Medicine, Mount Zion Hospital, San Francisco. 503 pages; 24 × 16 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $8.00.

Rosenau Preventive Medicine and Hygiene. 7th ed. By KENNETH F. MAXCY, M.D., Dr. P.H., Professor of Epidemiology, The Johns Hopkins University, School of Hygiene and Public Health. 1,462 pages; 25.5 × 17 cm. 1951. Appleton-Century-Crofts, Inc., New York. Price, $14.00.

711 Medical Maxims. By WILLIAM S. REVENO, M.D., Assistant Professor of Clinical Medicine, Wayne University Medical College, etc.; with Forewords by FREDERICK A. COLLER, M.D., and WILLIAM J. KERR, M.D. 197 pages; 16 × 12 cm. 1951. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.75.

Surgical Care: A Practical Physiologic Guide. By ROBERT ELMAN, M.D., F.A.C.S., Professor of Clinical Surgery, Washington University School of Medicine, etc. 586 pages; 25.5 × 17 cm. 1951. Appleton-Century-Crofts, Inc., New York. Price, $8.00.

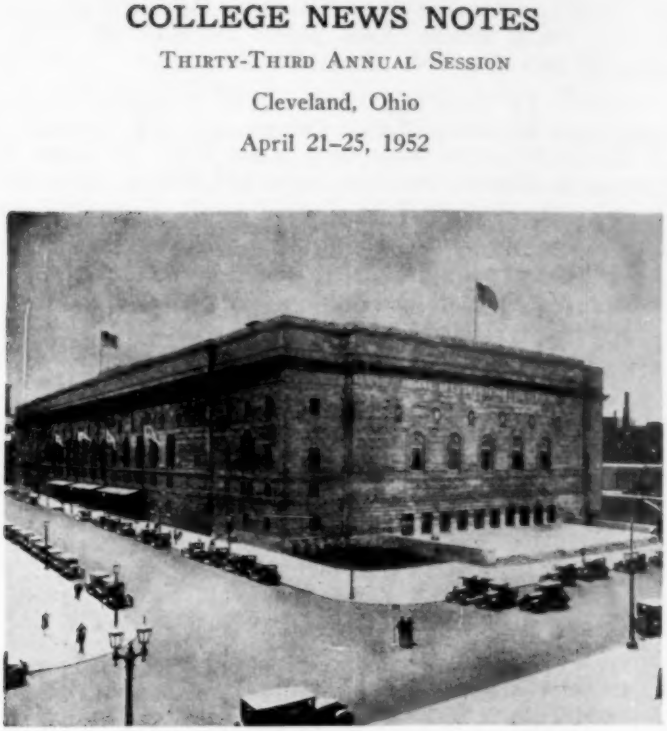
The Will to Live. By ARNOLD A. HUTSCHNECKER, M.D. 278 pages; 21 × 14 cm. 1951. Thomas Y. Crowell Company, New York. Price, $3.50.

COLLEGE NEWS NOTES

THIRTY-THIRD ANNUAL SESSION

Cleveland, Ohio

April 21–25, 1952



Public Auditorium, Cleveland, General Headquarters.

According to advance reports from President Maurice C. Pincoffs and General Chairman Roy W. Scott, great plans are about concluded for a superior program of Morning Symposia, General Sessions, Hospital Clinics, Color Televised Clinics and Clinico-Pathological Conferences for the forthcoming Annual Session of the College. All scientific sessions, with the exception of the Hospital Clinics, will be held in the Public Auditorium, where excellent facilities are available. Hospital Clinics will be held on Tuesday and Thursday mornings, terminating in time for physicians to return to the Auditorium for the Panel Discussions and Clinico-Pathological Conferences. There will be four concurrent Panel Discussions daily, Tuesday through Friday, and one series of Clinico-Pathological Conferences at the same time. A special bulletin will be published with the general program containing the protocols, and cases have been selected which will test the most clever diagnostician. There will be a program of Color Televised Clinics daily, Tuesday through Friday, in the mornings, televised from the Cleveland Clinic Hospital and shown at the Auditorium. On Wednesday and Friday mornings, the President has arranged two concurrent Symposia on subjects of timely and practical interest. General Sessions will be held from 2:00 p.m. to 5:00 p.m., Monday through Friday, in the Music Hall of the Auditorium. The Annual Business Meeting of Fellows and Masters and the election of Officers will take place on Thursday afternoon, just preceding the Fourth General Session. A program of entertainment has been arranged for both the men and the women. On Monday evening a concert by the Cleveland Orpheus Club, augmented with other

special talent, will be held in the Music Hall. On Wednesday evening there will be the Annual Convocation, to be addressed by the President of the College and Dr. Raymond B. Allen, F.A.C.P., President of the University of Washington. At the Convocation will be conferred not only Fellowships in course, but also the John Phillips Memorial Award, the James D. Bruce Memorial Award and the Alfred Stengel Memorial Award. On Thursday evening will be held the Annual Banquet of the College in the ballroom of the Hotel Statler. The Chairman of the Entertainment Committee assures us that the speaker who has been selected is one of the great orators of America.

The program of entertainment for the ladies has already been arranged, and will be one of the finest and most interesting ever put on for the College.

Although there will be no routine scientific exhibit, a large specialized cardiac demonstration will be put on in a special room at the Auditorium, under the direction of Dr. J. Scott Butterworth, F.A.C.P., Associate Professor of Medicine at the New York University-Bellevue Medical Center. Dr. Butterworth's demonstration will utilize three electron cardioscopes to provide three independent demonstrations.

The Technical Exhibit will be a larger and more varied one than has previously been arranged by the College. All exhibits, however, will be conducted on a high plane and restricted to products and services relevant to the practice of Internal Medicine and its allied specialties. Exhibitors are admitted by invitation and will be encouraged to hue closely to the high standards set by the Committee on Exhibits. Nowhere else in America can one find a Technical Exhibit of such proportions, covering the field of medical books, pharmaceuticals, equipment and other services which are all assembled for the information of the internist, with all irrelevant exhibits excluded.

Hotel Accommodations: The attendance at the Annual Sessions of the College has grown to such proportions that it is necessary to set up a Housing Bureau in connection with the Cleveland Convention and Visitors Bureau, 511 Terminal Tower, Cleveland 13, Ohio. A fully adequate number of good hotel rooms has been guaranteed, and a list of the hotels recommended will be published, along with rates, in a special reservation form, procurable from the Housing Bureau or from the Executive Offices of the College. It is anticipated that the preliminary program will be published in the February Issue of this Journal, and that the final program, which will contain a hotel reservation form, will be ready for distribution to all members of the College and to those on the mailing list before the end of February.

Cleveland Post-Convention "MARK TWAIN CRUISE"

So many members have been interested in a post-convention tour or cruise during the past two years and since the Bermuda Cruises following Annual Sessions of the past proved so enjoyable, it has been possible to arrange a MARK TWAIN CRUISE after the Cleveland meeting, leaving Cincinnati at 10:30 a.m., Saturday, April 26, 1951, and returning to Cincinnati on Saturday, May 2, 1951, sufficiently early to make all morning connections home by train or by air.

The Delta Queen, the best and largest in river service in the United States today, will be the cruise ship. With her unusual appointments, she sets a new standard in river travel. Half the staterooms have private bath and toilet, and many are air conditioned. All rooms are outside. The dining room is pleasant and air conditioned. The lounges and observation rooms are attractive and inviting. The decks are wide and call for exercise or loafing in the easy chairs, as one may desire. The total capacity is 204 passengers, with 104 in rooms with private bath. That means early decisions are necessary to get such rooms.

Why do we call this a Mark Twain Cruise? The steamer has many characteristics of the one with which Clemens was familiar; he knew the Ohio as well as the Mississippi River; those on the cruise will lead for a brief period the vagabonding life that Clemens knew and loved so well. Among the highlights of the route will be the run down the crooked Ohio, with its scores of ox-bow bends and lovely springtime scenery, to its junction with the Tennessee; then up that river, passing through the great Kentucky Lock and Dam, the highest single lock lift on the American Continent, into Kentucky Lake. This is one of the "Great Lakes of the South," the largest made by the TVA development and, in fact, the largest man-made lake in the world.

The Delta Queen.

Four shore excursions of unusual variety and interest will be made: a short visit to Cave-in-Rock, an old river pirate's den; a mint julep party while passing Paducah, the city of its birth; and a tour of the Mead Johnson plant in Evansville, internationally known makers of baby and dietary foods—this as a special courtesy to members of the College and their wives. Still another special courtesy has been extended by the National Distillers Corporation for a tour of one of its plants in Louisville. The tour of Louisville will include Churchill Downs where the most famous race in America, the Kentucky Derby, will be run on Saturday, May 3, 1951. The last shore excursion will include a tour of Madison, Ind., which, in many respects, resembles old Natchez, the Clifty Falls State Park, and a visit to the old Lanier Mansion, famous for its architectural beauty and the authenticity of its furnishings, one of Indiana's most treasured memorials.

The cruise will be in the charge of Mr. Leon V. Arnold, 36. Washington Square West, New York 11, N. Y., who has so successfully handled several post-convention events for the College. Write him for full particulars, ship plan, rates, complete itinerary, etc.

Down the Mississippi on the Robt. E. Lee.

New Elections to Membership, A.C.P.

At a meeting of the Board of Regents, Philadelphia, November 18, 1951, the following new elections took place (Fellows indicated in full CAPITALS; Associates in Lower Case):

Samuel E. Abel	Murfreesboro, Tenn. (V.A.)
Morris Alex	St. Louis, Mo.
Russell John Alleman	Portland, Ore.
Norman LaRue Anderson	Asheville, N. C.
GEORGE ELLIS ARMSTRONG	M. C., U. S. Army
John W. Armstrong	Hallettsville, Tex.
Myron Silver Arrick	San Francisco, Calif.
William James Atkinson, Jr.	Mobile, Ala.
LOUIS SHATTUCK BAER	Burlingame, Calif.
HARRY BALBEROR	Detroit, Mich.
Ruth Bernice Balkin	Gary, Ind.
David Ritch Barnum	Evanston, Ill.
Edgar Baron	Kecoughtan, Va. (V.A.)
ALFRED SIDNEY BARRITT, JR.	Brooklyn, N. Y.
FRANK RUDOLPH BARTA	Omaha, Nebr.
GEORGE WILLIAM BASCOM	Toledo, Ohio
Frederick Armour Beardsley, Jr.	Willimantic, Conn.
HERMAN BEERMAN	Philadelphia, Pa.
Eugene Huntington Benson, Jr.	El Centro, Cali.
Irving Besserglick	Cleveland, Ohio
Maurice McDonald Best, Jr.	Louisville, Ky.
Raymond James Bickerman	Peoria Heights, Ill.
Grosvenor Willse Bissell	Chicago, Ill.
FRANK WICKES BLATCHFORD, JR.	Winnetka, Ill.
MALCOLM BLOCK	Dayton, Ohio
Marvin Blum	Wilkes-Barre, Pa.
Martin Harold Boldt	Louisville, Ky.
Robert E. Bolinger	Kansas City, Kans.

PAUL KENNETH BOYER ..... Summit, N. J.
John Wilson Boylan ..... Buffalo, N. Y.
WILLIAM ALEXANDER BRAMS ..... Chicago, Ill.
MAYNARD BRANDSMA ..... Beverly Hills, Calif.
JOHN RUTLEY BRAUNSTEIN ..... Cincinnati, Ohio
Thomas Hamilton Bram ..... Long Beach, Calif. (V.A.)
NATHAN BROOKS ..... Detroit, Mich.
Arthur Edward Brown ..... Camp Hill, Pa.
Bradley Claude Brownson ..... San Mateo, Calif.
Hans J. Bruns ..... Syracuse, N. Y.
Marco Bruschi ..... Bakersfield, Calif.
ROBERT VAN ZANDT BUCKLIN ..... Saginaw, Mich.

GEORGE LLOYD CALVY ..... M. C., U. S. Navy
James Allan Campbell ..... Chicago, Ill.
Lloyd Albert Caswell ..... Montreal, Que., Can.
William Frank Cernock ..... Oak Park, Ill.
KENNETH WILLIAM CHAPMAN ..... U. S. Public Health Service
HENRY A. CHAPNICK ..... Detroit, Mich.
MAURICE RONOQUE CHASSIN ..... Maspeth, N. Y.
William Godfrey Childress ..... Valhalla, N. Y.
GEORGE EDWARD CLARK, JR. ..... Austin, Tex.
RAYMOND STANLEY CLARK ..... Los Angeles, Calif. (V.A.)
MARSHALL CLINTON, JR. ..... Buffalo, N. Y.
Harley Ernest Cluxton, Jr. ..... Chicago, Ill.
CHARLES WEST COFFEN ..... Portland, Ore.
Samuel Louis Cohen ..... Memphis, Tenn. (V.A.)
FRANCIS CARTER COLEMAN ..... Des Moines, Iowa
Eugene L. Coodley ..... Los Angeles, Calif.
Samuel Studdiford Cooley ..... Black Mountain, N. C.
EDWARD FRANCIS COTTER ..... Baltimore, Md.
Frederic Eugene Cowden ..... Nashville, Tenn.
LEELA STEVENS CRAIG ..... Berkeley, Calif.
LEO HERMANN CRIEP ..... Pittsburgh, Pa.
George Manning Cummins, Jr. ..... Chicago, Ill.
HAROLD G(OLDSMITH) CURTIS ..... Cleveland, Ohio
Paul Cutler ..... Atlantic City, N. J.
Seymour Saul Cutler ..... Brooklyn, N. Y.

Grayson Fairfax Dashiell ..... Kankakee, Ill.
William Anthony Davis ..... Glen Ridge, N. J.
John Edwin Dee ..... Worcester, Mass.
Norman Victor De Nosaquo ..... Chicago, Ill.
Robert Brooks Dickerson ..... M. C., U. S. Army
Marvin Merton Dickey ..... Elgin, Ill.
Victor Andre Digilio ..... Philadelphia, Pa.
Ivan C. Dimmick, Jr. ..... M. C., U. S. Army
Edmunds Grey Dimond ..... Kansas City, Kans.
HENRY HADLEY DIXON ..... Portland, Ore.
HERBERT VICTOR DOBSON ..... Peterborough, Ont., Can.
John Pell Doenges ..... Olney, Ill.
JOHN FRANK DRAPIEWSKI ..... Wilkes-Barre, Pa.
ABRAHAM AARON DUMANIS ..... Flushing, N. Y.
DONALD ALPHAEUS DUPLER ..... Philadelphia, Pa.

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Julius Elson ..... St. Louis, Mo.
Harry Jay Epstein ..... Philadelphia, Pa.
I(sadore) Selig Epstein ..... Philadelphia, Pa.

Robert Burnett Failey, Jr. ..... Indianapolis, Ind.
Stefan Stanislaus Fajans ..... Ann Arbor, Mich.
August Frederick Fath ..... Kalamazoo, Mich.
Donald Terrell Faulkner ..... Norfolk, Va.
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Mack Henry Fieber ..... New York, N. Y.
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James Stanton Tipping ..... Pittsburgh, Pa.
Thomas Bell Tooke, Jr. ..... Shreveport, La.
Walter J. Trautman, Jr. ..... New Orleans, La.
JOHN BUFFINGTON TREDWAY ..... Erie, Pa.
Philip R. Trommer ..... Philadelphia, Pa.
Robinson Marshall Truitt, Jr. ..... Philadelphia, Pa.

MILTON HARMOND UHLEY ..... Beverly Hills, Calif.

J. RAY VAN METER ..... Palo Alto, Calif.
Carl Frederick Vilter ..... Cincinnati, Ohio

W(ILLIAM) WAYNE WADDELL ..... Beatrice, Nebr.
RALPH THOMAS WARBURTON ..... North Canton, Ohio
Merna Mary Warne ..... Prescott, Ariz. (V.A.)
Samuel Edward Warshauer ..... Wilmington, N. C.
Peter J. Washko ..... Honolulu, T. H.
Leslie Richard Webb, Jr. ..... Springfield, Mo.
Herman Weiner ..... Beverly Hills, Calif.
Jerome Weiss ..... New York, N. Y.
James Leroy Wells ..... Orangeburg, S. C.
Robert Darwin Westphal ..... Houston, Tex. (V.A.)
Claude Benjamin White ..... M. C., U. S. Air Forse
James Arista Wier ..... M. C., U. S. Army
ABBOTT YATES WILCOX, JR. ..... Bay Pines, Fla. (V.A.)
George Dee Williams ..... Buffalo, N. Y. (V.A.)
Benjamin Norman Wilson ..... Tyler, Tex.
JOSEPH McMILTON WILSON ..... Dayton, Ohio
John Charles Wilt ..... Winnipeg, Man., Can.
ROBERT ALLEN WISE ..... Houston, Tex. (V.A.)
William Wolarsky ..... New York, N. Y.
BENJAMIN H. WOLFMAN ..... San Francisco, Calif.

Mark Atche Yessian ..... Providence, R. I.
JOHN DAVID YOUNG, JR. ..... Memphis, Tenn.
ROBERT ARMSTRONG YOUNGMAN ..... Lincoln, Nebr.

DANIEL WESTON ZAHN ..... Seattle, Wash.
Morris Zuckerbrod ..... Brooklyn, N. Y.

PROPOSED SCHEDULE OF A.C.P. POSTGRADUATE COURSES, SPRING OF 1952

GASTRO-ENTEROLOGY: University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.; Theodore L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Directors; one week, February 25–29, 1952.

This course will be a repetition, with revisions, of the course given by Drs. Althausen and Wilbur for the College during the Spring of 1949. It will give a survey of recent developments in gastro-enterology and emphasis will be placed on gastrointestinal physiology, biochemistry and pathology. The course will comprise didactic presentations, conferences, case presentations and panel discussions. The faculty will be selected from the two coöperating medical schools and supplemented by a few outstanding authorities from other institutions.

CURRENT CONCEPTS OF ALLERGY AND ASSOCIATED DISORDERS: Washington University School of Medicine, St. Louis, Mo.; Harry L. Alexander, M.D., F.A.C.P., Director; one week, March 3–7, 1952.

This course is designed primarily for those interested in the broad aspects of human hypersensitiveness according to present thought. It will include a wide variety of disorders, resulting from antigen-antibody reactions, which, instead of conferring protection, induce many clinical syndromes. This main mechanism underlies bronchial asthma, the allergic aspect of infectious diseases, drug sensitiveness, serum sickness, transfusion reactions and other hematological abnormalities. The relation of allergy to collagen diseases, as periarteritis nodosa and others that respond to ACTH, will be considered. Although emphasis will be placed on clinical aspects, underlying mechanisms will be elaborated.

DISEASES OF THE BLOOD VESSELS: Cornell University Medical College and New York Hospital, New York, N. Y.; Irving S. Wright, M.D., F.A.C.P., Director; one week, March 10–15, 1952.

This course first appeared on the College schedule during the Spring of 1950 and was one of the most popular courses of the year. The course is designed to present a review of the present knowledge regarding diseases of the blood vessels from the head to the feet, but excluding the heart. It is especially directed to internists, cardiologists and practitioners of general medicine who feel the need for additional information in this field. While basic concepts will not be neglected, emphasis will be placed on clinical problems and how they can be met. Some sessions will be in the form of special symposia dealing with key aspects of this great field; and these will be followed by question and answer periods in which the matriculates will be encouraged to participate freely. Patient presentation and case studies, wherever feasible, and recent advances in treatment will receive emphasis.

CLINICAL MEDICINE FROM THE HEMATOLOGICAL VIEWPOINT: Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director; one week, March 17–22, 1952.

This course has been given on several previous occasions, the last one during the Spring of 1949. The course has always been an outstanding one. The course is planned for those interested primarily in internal medicine who desire a more intimate and detailed acquaintance and first-hand familiarity with the range of newer technics for the accumulation of fundamental hematologic data, and a better understanding of the bases for their interpretation and translation into clinical management and specific therapy. Lectures, clinics, conferences, practical demonstrations, panel and general discussions, informal personal conferences, individual laboratory microscopic work. Registrants are urged to bring their own microscopes.

INTERNAL MEDICINE: University of Michigan Medical School, Ann Arbor, Mich.; Cyrus C. Sturgis, M.D., F.A.C.P., Director; one week, date to be announced.

This is a repetition of a very popular course in the general field of internal medicine given on several previous occasions under Dr. Sturgis' direction.

ELECTROCARDIOGRAPHY—BASIC PRINCIPLES AND INTERPRETATION: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., one week, date to be selected.

This course in Electrocardiography has appeared more or less regularly on the College schedule for some years, and represents one of the fine courses in its field. It is designed to acquaint the student of that subject with modern theory and its clinical application. The opening days will consist of lectures on the theory of electrocardiography and an attempt will be made to present the current points of view. The course will be limited to those who have had some previous experience in the field. By presenting many electrocardiograms from the laboratory, there will be sufficient material to cover the most important representative patterns. The chief aim of the course will be to teach interpretation based on current knowledge of the physiology of heart muscle. All exercises in practical interpretation will include the new leads.

TRENDS AND NEWER DEVELOPMENTS IN INTERNAL MEDICINE: Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa.; Charles L. Brown, M.D., F.A.C.P., Director; one week, dates to be announced.

This will be a general course in internal medicine for which the faculty will be selected not only from Hahnemann Medical College but from all of the medical schools in Philadelphia with some distinguished guest teachers from the East. Details of this promising course will be published in due course.

PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE: University of Toronto Faculty of Medicine, Toronto, Ont.; Ray F. Farquharson, M.D., F.A.C.P., Director; one week, date to be announced.

It has been the policy of the College to give this particular course in various medical centers. The course was first organized and initiated by Dr. Julius H. Comroe, Jr., F.A.C.P., of the Graduate School of Medicine of the University of Pennsylvania. Under the same title courses have been given by Dr. A. C. Ivy, F.A.C.P., of the University of Illinois, and Dr. Eugene A. Stead, Jr., F.A.C.P., of Duke University School of Medicine. The Committee has long planned to have the course put on by one of the prominent Canadian medical schools. This course has always attracted a large registration.

The above schedule is subject to slight possible change, but the College will have eight courses on its schedule for the Spring and has one or more alternate courses held in reserve. The Postgraduate Bulletin, containing all details, faculty personnel, etc., will be published early in the new year and sent, with registration forms, to all members of the College and to non-members who have requested their names to be placed on the mailing list.

On the recommendation of the Advisory Committee on Postgraduate Courses, the Board of Regents, on November 18, 1951, approved of the following courses which may be scheduled at some future date:

RHEUMATIC DISEASES—Walter Bauer, M.D., F.A.C.P., Director, Boston, Mass.

INTERNAL MEDICINE—Ward Darley, M.D., F.A.C.P., Director, Denver, Colo.

INTERNAL MEDICINE—Paul Starr, M.D., F.A.C.P., Director, Los Angeles, Calif.

*HEMATOLOGY—William Dameshek, M.D., F.A.C.P., Director, Boston, Mass.

*INTERNAL MEDICINE or HEMATOLOGY—M. M. Wintrobe, M.D., F.A.C.P., Director, Salt Lake City, Utah.

*GASTRO-ENTEROLOGY—Henry L. Bockus, M.D., F.A.C.P., Director, Philadelphia, Pa.

*CLINICAL ALLERGY—Robert A. Cooke, M.D., F.A.C.P., Director, New York, N. Y.

*PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE—Eugene A. Stead, Jr., M.D., F.A.C.P., Director, Durham, N. C.

*INTERNAL MEDICINE—R. R. Snowden, M.D., F.A.C.P., Director, Pittsburgh, Pa.

*CARDIOVASCULAR DISEASE—William G. Leaman, Jr., M.D., F.A.C.P., Director, Philadelphia, Pa.

*INTERNAL MEDICINE—William S. Middleton, M.D., F.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Directors, Madison, Wis.

*CARDIOVASCULAR DISEASE—Louis N. Katz, M.D., F.A.C.P., Director, Chicago, Ill.

*CARDIOVASCULAR DISEASE—George C. Griffith, M.D., F.A.C.P., Director, Los Angeles, Calif.

*CARDIOVASCULAR DISEASE—Clarence E. de la Chapelle, M.D., F.A.C.P., Director, New York, N. Y.

*DISEASES DUE TO ALLERGIC AND IMMUNE MECHANISMS—Leo H. Criep, M.D., F.A.C.P., Director, Pittsburgh, Pa.

*INTERNAL MEDICINE—Howard P. Lewis, M.D., F.A.C.P., Director, Portland, Ore.

* Courses that have been given previously.

*Electrocardiography—Gordon B. Myers, M.D., F.A.C.P., Director, Detroit, Mich.

*Internal Medicine—Garfield G. Duncan, M.D., F.A.C.P., Director, Philadelphia, Pa.

*Peripheral Vascular Disease or Internal Medicine—Mayo Clinic, Rochester, Minn.

*Internal Medicine—Stacy R. Mettier, M.D., F.A.C.P., Director, San Francisco, Calif.

*Dynamic Therapeutics of Chronic Diseases—Howard A. Rusk, M.D., F.A.C.P., Director, New York, N. Y.

Internal Medicine—David P. Barr, M.D., F.A.C.P., Director, New York, N. Y.

Psychosomatic Medicine (under an appropriate title)—Harold G. Wolff, M.D., F.A.C.P., and Stewart G. Wolf, Jr., M.D., Co-directors, New York, N. Y.

Electrocardiography—Charles Kossmann, M.D., F.A.C.P., Director, New York, N. Y.

Hematology—Howard L. Alt, M.D., F.A.C.P., Louis R. Limarzi, M.D., F.A.C.P., and Leon O. Jacobson, M.D., F.A.C.P., Co-directors, Chicago, Ill.

Psychosomatic Aspects of Internal Medicine—William C. Menninger, M.D., F.A.C.P., Director, Topeka, Kans.

Pathology of Internal Medicine—Balduin Lucké, M.D., Director, Philadelphia, Pa.

Cardiology—Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-directors, New York, N. Y.

Internal Medicine—Maurice C. Pincoffs, M.D., M.A.C.P., Director, Baltimore, Md.

A number of the above courses will be selected for the Autumn Schedule of 1952, and others will be selected for schedules to follow.

Forthcoming A.C.P. Regional Meetings

Territory	City	Date	A.C.P. Governor	Special Guest(s)
Colorado	Denver	February 12	Ward Darley, M.D.	Dwight L. Wilbur, M.D., San Francisco, Regent, A.C.P.
Midsouth (La., Miss., Tenn., Tex.)	New Orleans	February 15	Thomas Findley, M.D.	M. C. Pincoffs, M.D., Baltimore, President, A.C.P. E. R. Loveland, Executive Secretary
Puerto Rico	San Juan	February 17	R. Rodriguez-Molina, M.D.	T. Grier Miller, M.D., Philadelphia, President Elect, A.C.P.
Nebraska	Lincoln	February 23	J. D. McCarthy, M.D.	Pending
Virginia	Charlottesville	February 28	Charles M. Caravati, M.D.	E. R. Loveland, Executive Secretary
Maryland, District of Columbia and Delaware	Baltimore	March 1	R. Carmichael Tilghman, M.D.	M. C. Pincoffs, M.D., Baltimore, President, A.C.P.
Kansas	Emporia	March 21	William C. Menninger, M.D.	M. C. Pincoffs, M.D., Baltimore, President, A.C.P.

The following regional meetings for the Autumn of 1952 are already scheduled: New Jersey at Newark, November 5; Midwest (Illinois, Indiana, Iowa, Michigan,

Minnesota, Ohio and Wisconsin) at Chicago, November 22; Southeastern (Alabama, Florida, Georgia, South Carolina and Cuba) at Havana, November —.

A.C.P. Southeastern Regional Meeting to Be Held in Havana, Cuba, 1952

The Southeastern Regional Meeting district includes Alabama, Florida, Georgia, South Carolina and Cuba. Its 1951 Regional Meeting was held at Jacksonville, Fla., November 2–3. Dr. William C. Blake, F.A.C.P., Governor for Florida was the General Chairman. Dr. Turner Z. Cason, F.A.C.P., former Governor for Florida, and the Governors for Alabama, Georgia, South Carolina and Cuba, Drs. E. Dice Lineberry, F.A.C.P., Carter Smith, F.A.C.P., Robert Wilson, Jr., F.A.C.P., and José J. Centurión, F.A.C.P., respectively, arranged a superb program, one that would do credit to any national meeting. Dr. Edward L. Bortz, Philadelphia, a Regent of the College, gave a stimulating and inspiring address, "The Challenge of Growth," at the banquet.

The Governors and the College members accepted the invitation of Dr. Angel Vieta, F.A.C.P., who substituted for Governor Centurión of Cuba, to hold the 1952 Regional Meeting at Havana. This will be a featured regional meeting on the 1952 schedule and all members of the College and their guests, whether from the Southeastern district or not, are cordially invited to attend. The date will be announced soon, but it is anticipated the meeting will be held during November.

Meetings of the Committee on Credentials, A.C.P.

The Committee on Credentials of the American College of Physicians will meet at Philadelphia on March 16 and at Cleveland on April 19, 1952. Proposals for membership must be received at the College Headquarters sixty days in advance of action, or by January 16 and February 19, 1952, respectively.

The next succeeding meeting of the Committee on Credentials will not occur until November, 1952.

American Board of Pediatrics Examinations

The American Board of Pediatrics has announced the following oral examinations for 1952:

New York, N. Y.—February 1, 2, 3, 1952
St. Louis, Mo.—April, 1952

Laboratory Refresher Training Courses

The Communicable Disease Center of the U. S. Public Health Service, Chamblee, Ga., has announced a schedule of laboratory training courses to be given by the Communicable Disease Center during the year 1952. The courses are designed for laboratory directors, senior laboratory staff members, physicians and others of comparable professional standing. The length of the course varies from one to four weeks, and includes such subjects as Serology of Syphilis, Laboratory Diagnosis of Bacterial Diseases, Laboratory Diagnosis of Parasitic Diseases, Laboratory Diagnosis of Virus Diseases, Laboratory Methods in Medical Mycology, Laboratory Diagnosis of Rabies, Laboratory Diagnosis of Tuberculosis, Laboratory Methods in the Study of Pulmonary Mycoses, Laboratory Diagnosis of Malaria, Identification of Medically Important Arthropods, Virus Isolation and Identification Technics, Laboratory Diagnosis of

Influenza, Typing of *Corynebacterium diphtheriae*, Special Problems in Enteric Bacteriology, Phage Typing of *Salmonella typhosa*, and Serologic Diagnosis of Rickettsial Diseases.

Information and application forms may be obtained from the Chief, Laboratory Training Services, Communicable Disease Center, U. S. Public Health Service, P. O. Box 185, Chamblee, Ga.

The National Institute of Neurological Diseases and Blindness of the Public Health Service, in addition to awarding research grants and fellowships, now has funds available for traineeships in the field of rehabilitation.

These traineeships are to be awarded to those who are qualified and interested in the principles and practice of total rehabilitation of the disabling diseases. Traineeships will be extended to neurologists, psychiatrists, orthopedists, pediatricians, internists and other professional personnel. Training will be conducted in recognized rehabilitation centers throughout the country.

All inquiries should be addressed to Dr. Pearce Bailey, Director of the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

"Metabolism—Clinical and Experimental" is the title of a new journal being instituted by Grune and Stratton of New York City. The journal will be devoted to nutrition, endocrines, genetics, dystrophies, diabetes and gout. The Editor-in-chief is Dr. Samuel Soskin, F.A.C.P., Chicago, Ill., and the Consulting Editor, Dr. Fuller Albright, Boston, Mass. Among the Associate Editors appear the names of Dr. Edwin B. Astwood, F.A.C.P., Boston, Mass., Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, Pa., Dr. R. F. Farquharson, F.A.C.P., Toronto, Canada, Dr. Norman Jolliffe, F.A.C.P., New York, N. Y., and Dr. Herbert Pollack, F.A.C.P., New York, N. Y.

Dr. John Minor, F.A.C.P., Washington, D. C., retired as President of the American Clinical and Climatological Association at its meeting at Skytop, Pa., during November and was succeeded by Dr. Chester Jones, F.A.C.P., Boston, Mass.

Rear Admiral Joel J. White, (MC), U.S.N., Retired, F.A.C.P., heretofore Medical Director and Administrator of the Nashville (Tenn.) Regional Blood Center, has accepted the position of Medical Director of St. Mary's Hospital at Knoxville, Tenn. Among his duties will be the organization of interne and resident training to meet the approval of the Council on Medical Education and Hospitals of the American Medical Association.

The Association of American Medical Colleges held its annual meeting October 29–31 at French Lick Springs, Ind. Dr. Rudolph H. Kampmeier, F.A.C.P., Nashville, Tenn., was Chairman of the round-table discussion, "Regional Hospital Plans and Continuation Education of Physicians"; Dr. Richard H. Young, F.A.C.P., Chicago, Ill., was chairman of the discussion, "The Threat of Large-Scale Research Programs to the Quality of Medical Education"; and Dr. David P. Barr, F.A.C.P., New York, N. Y., was Chairman of the discussion, "Medical Teaching on the Ambulant Patient."

Dr. Hobart A. Reimann, F.A.C.P., Philadelphia, Pa., has resigned as Magee Professor of Medicine and Head of the Department of Experimental Medicine at Jefferson Medical College of Philadelphia. Dr. Reimann recently addressed a meeting of the Ottawa Academy of Medicine on "Prolonged Fever and Viral Dysentery."

Dr. Samuel M. Feinberg, F.A.C.P., Professor of Medicine, Northwestern University Medical School, Chicago, was chosen President-Elect of the International Association of Allergology, which was recently organized and held its first meeting at Zurich, Switzerland, September 23–29. The Association plans to hold its next meeting at Rio de Janeiro in 1955.

The Bridgeport (Connecticut) Heart Association conducted a seminar in Cardiovascular Disease on December 5, 1951. Dr. Sidney L. Penner, F.A.C.P., was the Program Chairman, Dr. Marcus Backer, F.A.C.P., and Dr. I. Sidney Zaur, F.A.C.P., were Presiding Officers and the following Fellows presented papers: Dr. William Resnik, Stamford, "Atypical Forms of Angina Pectoris"; Dr. Henry Dolger, New York, "Diabetes and Vascular Disease"; Dr. Louis H. Nahum, New Haven, "Clinical Experiences with Some of the Newer Cardiac Drugs"; Dr. A. Wilbur Duryee, New York, "The Management of Occlusive Arterial Disease."

The Du Page County (Illinois) Health Department dedicated its Annual Report for 1951 to Dr. Arthur Sterling Webb, F.A.C.P., in recognition of his support and counsel during his six-year term as Chairman and for his being responsible for the growth and prestige of Public Health in Du Page County. Dr. Webb is on the National and State Boards of the National Tuberculosis Association.

The following Fellows of the College participated on the Scientific Program of the 5th District Medical Society's Annual Fall Meeting at the North Carolina Sanatorium, McCain, N. C., November 15, 1951: Dr. Charles H. Burnette, newly appointed Professor of Medicine at the University of North Carolina, and Dr. J. L. Callaway, Head of the Department of Dermatology at Duke Hospital. Dr. J. S. Hiatt, Jr., F.A.C.P., was reëlected Secretary-Treasurer, and also Counselor for the 5th District; Dr. Robert McMillan, F.A.C.P., was elected Alternate Counselor. The Counselors from each of the ten districts comprise the Executive Committee for the Medical Society of the State of North Carolina.

Dr. Randall G. Sprague, F.A.C.P., Rochester, Minn., spoke on "Physiologic Effect of Cortisone and Corticotropin (ACTH)" at the annual meeting of The Central Neuropsychiatric Association, Minneapolis, Minn., October 19–20.

Dr. Horst A. Agerty, F.A.C.P., was recently appointed Chief of the Pediatrics Department of St. Luke's and Children's Medical Center, Philadelphia.

The Fifth Annual William Allen Pusey Memorial Lecture of the Institute of Medicine of Chicago was delivered by Dr. John H. Talbott, F.A.C.P., Professor of Medicine at the University of Buffalo School of Medicine, on October 22. Dr. Talbott's subject was "Experimental Observations in Acute and Chronic Gout."

Dr. John B. Levan, F.A.C.P., Reading, was elected President-Elect of the Pennsylvania Heart Association at its meeting during November at Philadelphia.

Among the speakers at the centennial meeting of the Polk County Medical Society, which was held in Des Moines, Iowa, on October 24, were Dr. Carl V. Moore, F.A.C.P., St. Louis, Mo., "Advances in Our Knowledge of the Anemias"; Dr. Walter

L. Bierring, F.A.C.P., Des Moines, Iowa, "Medical Pioneers of Polk County"; and Dr. George F. Lull, F.A.C.P., Chicago, Ill., "Progress in Medicine."

Dr. Harold F. Himwich, F.A.C.P., Chief of the Clinical Research Division, Chemical Corps Medical Laboratories, Army Chemical Center in Maryland, has been appointed Director of the Research Division of the Galesburg (Ill.) Cottage Hospital.

Dr. William B. Castle, F.A.C.P., Director of the Thorndike Memorial Laboratory and Professor of Medicine at the Harvard Medical School, delivered the Fourth Annual Harvard Lecture at the University of Colorado Medical Center, Denver, on November 9. His subject was "Red Cell Destruction in Hemolytic Anemias."

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, has been appointed coordinator of teaching in cardiology by the Southeastern Pennsylvania Heart Society.

Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., was elected Chairman of the Section on Diseases of the Chest of the American Medical Association at its last meeting in Atlantic City, N. J., in June, 1951.

Dr. Pascal F. Lucchesi, F.A.C.P., Philadelphia, Pa., recently received the annual award of the Pennsylvania Public Health Association for "Meritorious Work in Public Health," in recognition of his work and interest in public health for Pennsylvania.

The Federal Government has announced plans for a hospital for Osceola, Ark., and it is expected that construction will probably begin next summer. In making this announcement, Dr. Lorenzo D. Massey, F.A.C.P., Chairman of the Hospital Committee of the Osceola Chamber of Commerce, said that the hospital will cost approximately $540,000, will contain forty beds and be constructed so that it can be expanded if necessary.

The American Society for the Study of Arteriosclerosis held its annual meeting in Chicago, Ill., November 4–5, under the presidency of Dr. E. Cowles Andrus, F.A.C.P., Baltimore, Md. Among the guest speakers were Dr. Joseph B. Wolffe (Associate), Philadelphia, Pa., who spoke on "Methonium Compounds in the Treatment of Essential Benign and Malignant Hypertension Before and After Sympathectomy."

At the annual meeting of the Oregon State Medical Society held in Portland, October 10–13, Dr. Robert F. Miller (Associate), Portland, was reëlected Secretary.

Among the guest speakers at the scientific assembly of The New York State Academy of General Practice, which was held in New York, October 29–31, were five Fellows of The American College of Physicians: Dr. Philip S. Hench, Rochester, Minn., "Status in Clinical Medicine"; Dr. Chester S. Keefer, Boston, Mass., "Antibiotics"; Dr. Walter C. Alvarez, Chicago, Ill., "Causes of Great Nervousness"; Dr. Wingate M. Johnson, Winston-Salem, N. C., "Geriatrics"; and Dr. Elmer L. Sevringhaus, Nutley, N. J., "The Obese Patient."

Dr. William D. Robinson, F.A.C.P., Director of the Rackham Arthritis Research Unit of the University of Michigan, delivered the annual Ralph Pemberton Memorial Lecture on October 25, at the Philadelphia County Medical Society. His subject was "Gouty Arthritis."

At the recent annual meeting of the Washington State Medical Association, Dr. Bruce Zimmerman, F.A.C.P., Seattle, was elected Secretary-Treasurer.

The American Cancer Society has announced the appointment of Dr. William H. Stoner, F.A.C.P., as Assistant to the Medical and Scientific Director. Among Dr. Stoner's duties will be that of Executive Editor of *"CA–A Bulletin of Cancer Progress."*

Dr. Paul B. Beeson, F.A.C.P., Atlanta, Ga., spoke on "Evaluation of Clinical Importance of Corticotropin (ACTH) and Cortisone," at the annual meeting of the Georgia Academy of General Practice held in Macon on October 25.

In honor of his 18 years as Head of the Department of Internal Medicine at the University of Illinois, Dr. Robert W. Keeton, F.A.C.P., was tendered a dinner on October 4, attended by over four hundred persons. A commemorative volume, consisting of 36 original scientific papers written by his colleagues, former students, and friends was presented to Dr. Keeton.

Dr. Howard R. Sauder, F.A.C.P., Wheeling, was elected President of the West Virginia Heart Association at its annual meeting held in Morgantown on October 5.

Among the guest speakers at the annual meeting of The Gulf Coast Clinical Society, held in Edgewater Park, Miss., October 18–19, under the presidency of Dr. Wesley W. Lake, F.A.C.P., were Dr. Priscilla White, F.A.C.P., Boston, Mass., "Management of Complications of Diabetes," and Dr. Edgar Jones, F.A.C.P., Nashville, Tenn., "Problems in Diagnosis of Anemia."

Dr. William Saphir, F.A.C.P., Chicago, Ill., was recently appointed Clinical Assistant Professor of Medicine at the University of Illinois College of Medicine.

Among the guest speakers at the Nineteenth Annual Assembly of the Omaha Mid-West Clinical Society, which was held in Omaha, October 29–November 2, were nine Fellows of The American College of Physicians. They were: Dr. Louis H. Bauer, Hempstead, N. Y., President-Elect of the American Medical Association, "The Financial Problems of Medical Education"; Dr. Edward W. Boland, Los Angeles, Calif., "The Use of Adrenal Cortical Steroids and Anterior Pituitary Adrenocorticotropic Hormone in the Treatment of Rheumatic Diseases"; Dr. Arthur Grollman, Dallas, Tex., "Treatment of Anemia"; Dr. Lewis N. Katz, Chicago, Ill., "Recent Developments in Cardiovascular Diagnosis"; Dr. Roland P. Mackay, Chicago, Ill., "Clinical Neurology of the Spinal Cord"; Dr. Louis R. Limarzi, Chicago, Ill., "Multiple Myeloma: Diagnostic and Therapeutic Aspects"; Dr. Frank J. Heck, Rochester, Minn., "The Wasted Effort Expended in Arriving at Final Diagnosis of Blood Dyscrasias"; Dr. Theodore L. Squier, Milwaukee, Wis., "Clinical Manifestations of Antigen-Antibody Reactions in Blood Cells"; and Dr. Maxwell M. Wintrobe, Salt Lake City, Utah, "Diagnosis and Treatment of the Anemias."

Dr. W. Edward Chamberlain, F.A.C.P., Professor of Radiology, Temple University School of Medicine, Philadelphia, delivered the annual Leo G. Rigler Lecture at the University of Minnesota Medical School, November 1. His topic was "Recent Advances in Equipment for Fluoroscopy."

Dr. Frederick G. Gillick, F.A.C.P., was recently appointed Dean of Creighton University School of Medicine, Omaha, Nebr.

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, Pa., spoke on "Peptic Ulcer" at the second annual scientific assembly of the Nassau County Chapter of the American Academy of General Practice, held November 14 in Garden City, N. Y.

Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, was recently reëlected Secretary-Treasurer of the Medical Society of the State of Pennsylvania.

Among the guest speakers at the twenty-third annual Stuart McGuire Lecture Series and a symposium on Cardiology, held November 7–9 at the Medical College of Virginia, were: Dr. George E. Burch, F.A.C.P., New Orleans, La.; Dr. Harold Feil, F.A.C.P., Cleveland, Ohio; and Dr. Irving S. Wright, F.A.C.P., College Governor for Eastern New York.

At the recent meeting of The American Congress of Physical Medicine held in Denver, Colo., Dr. Walter M. Solomon, F.A.C.P., Cleveland, Ohio, was named President-Elect and Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., was elected Treasurer.

OBITUARIES

DR. HENRY ASBURY CHRISTIAN

Dr. Henry Asbury Christian, A.B., A.M., M.D., LL.D., Sc.D., F.R.C.P. (C.), (Hon.), of Brookline, Massachusetts, Master of the American College of Physicians, died in Whitefield, New Hampshire, on August 24, 1951, of a coronary thrombosis. Born in Lynchburg, Virginia, February 17, 1876, Dr. Christian attended the public schools there and at 16 entered Randolph-Macon College, receiving his A.B. and A.M. degrees in 1895 at the age of 19. After a year of postgraduate work, he was admitted to the Johns Hopkins University Medical School, graduating in 1900. For the next five years, Dr. Christian was a member of the Department of Pathology of Harvard University, the Childrens' Hospital of Boston and the Boston City Hospital. In 1903, he received a Master of Arts degree from Harvard University. In 1905, he became Instructor in the Theory and Practice of Physic at Harvard Medical School and was an assistant in charge of clinical teaching there. It was during this period that the clinical clerkship in medicine was introduced as an elective course and Dr. Christian was in charge under the supervision of Dr. R. H. Fitz, then Hersey Professor of the Theory and Practice of Physic. In 1907, Dr. Christian became Physician-in-Chief of the Carney Hospital and, the next year, Hersey Professor of Theory and Practice of Physic and Dean of the Faculty of Medicine of the Medical School at Harvard. The former position he held until his retirement in 1939, and the Deanship until 1912, his first year of active duty as Physician-in-Chief at the Peter Bent Brigham Hospital. It is said that Dr. Christian was affectionately called the "boy" dean, having been only 32 years old when he was appointed to that post at the Harvard Medical School.

President Eliot is said to have been impressed by Dr. Christian's capacity to think clearly and to express himself forcefully on the occasion when he heard Dr. Christian make an impromptu speech. His appointment as Dean followed shortly thereafter. In spite of Dr. Christian's age the President, Fellows and Overseers of Harvard University had confidence in his ability as Dean well justified by the results, the five years of his tenure as Dean being marked by notable improvements in the opportunities for medical education and medical research.

From the time when the Peter Bent Brigham opened its doors to patients in 1913 until 1939, a period of 26 years, Dr. Christian was its Physician-in-Chief. Within a few years after the wards of the Brigham Hospital were opened, it became widely known as one of the outstanding clinics of the world. Many physicians and medical students received their training in internal medicine there under Dr. Christian's guidance, a good number later becoming leaders in American medicine. All of them were profoundly influenced by the leadership of Professor Christian, who looked upon them as his "boys" and was, in turn, affectionately called "Uncle Henry," or "The Professor." In 1936, on the occasion of his sixtieth birthday, his associates and house officers, present and past, dedicated to him as Physician and Teacher a volume of medical papers. It was a fine tribute, as well as an example of the type of work that Dr. Christian had stimulated while Chief of the Brigham.

During World War I, Dr. Christian was a Major in the Medical Reserve Corps, U. S. A. During World War II and after his retirement from active duty at the Peter Bent Brigham Hospital and the Harvard Medical School, Dr. Christian was, from 1942-1946, Clinical Professor of Medicine at Tufts College Medical School and Visiting Physician at the Beth Israel Hospital, where he continued to teach medical students, make ward visits and take an active part in the training of young physicians.

Very active as an author and editor, Dr. Christian was many times honored by the awarding of honorary degrees. Jefferson Medical College and the University of Michigan both conferred upon him a Doctor of Science degree and Western Reserve University gave him an honorary Doctor of Laws degree. The American Medical Association awarded him their Distinguished Service Medal and the Royal College of Physicians of Canada conferred an honorary Fellowship. At some time he was President of the Association of American Physicians, President of the American Society for Clinical Investigation and President of the Interstate Postgraduate Medical Association. His interest in clinical medicine continued to the end. As recently as May, 1951, he read a paper before the Association of American Physicians, *Acute Pericarditis of Unknown Cause,* and he went on with his editorial work and writing for the Oxford Monograph Series until his death.

Dr. Christian made many contributions to medical education and to medical practice. He led and stimulated young men to search for the truth. He was held in the highest esteem and respect by all who had the privilege of being associated with him. His loyalty to his men was never doubted and his standards of conduct and performance were exceedingly high. Many who knew Dr. Christian only slightly considered him to be austere and a few were somewhat frightened by his manner. His warm heart, generous spirit and great human understanding were recognized by all of his close friends and associates. Those who knew him best will miss him most —but American Medicine will miss him most of all. For his service and example to medicine, to which he devoted his life, physicians owe him a separate debt—one that may be repaid in part by following the fine example set by him.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

CAPTAIN OMAR JESSE BROWN

Captain Omar Jesse Brown, Medical Corps, USN, died on July 7, 1951, in Georgetown Hospital, Washington, D. C. He was laid to rest with full military honors in Arlington National Cemetery on July 10. At the time of his death, Captain Brown was on active duty and was one of the foremost authorities on tropical medicine in the Medical Department of the Navy.

Captain Brown, the staff medical officer of the Fleet Marine Force, Atlantic, suffered a fractured back in an accidental fall down a flight of steps in his home at Norfolk, Va., on June 10. He was brought to Washington, D. C., for treatment on June 21, and died of complications resulting from the fall.

Born in Bombay, N. C., on July 30, 1902, he received his degree of Doctor of Medicine from George Washington University School of Medicine in 1929. In the same year he was commissioned a Lieutenant (junior grade) in the Medical Corps of the Navy and served his internship at the Naval Hospital, Washington, D. C.

Following various assignments, ashore and afloat, he was responsible for reducing the incidence of malaria at Marine Corps installations in North Carolina during 1941–43. For his outstanding performance of duty during this period he received a Commendation from the Secretary of the Navy. From 1943–45 he was in charge of the Navy's epidemic disease control board at the Bureau of Medicine and Surgery. Captain Brown, during World War II, was also engaged in similar work in the Pacific.

In addition to the Commendation Ribbon, Captain Brown was awarded the following Medals and Awards: The American Defense Service Medal, American Area Medal, Asiatic-Pacific Area Medal, Philippine Liberation Medal and the World War II Victory Medal.

He was a member of the American Medical Association, a Fellow of the American College of Physicians (since 1943), a Diplomate of the American Board of Pathology and a member of the Theta Delta Chi Fraternity.

Surviving are his wife, Mrs. Audrey A. Brown, two daughters, Miss Joanne Harlow Brown and Miss Beverley Andrea Brown, and his parents, Mr. and Mrs. Vernon L. Brown.

Prepared by the Bureau of Medicine and Surgery
Department of the Navy

DR. ALBERT MARSEE LUPTON

Dr. Albert Marsee Lupton, an Associate of the American College of Physicians, Philadelphia, Pa., died June 28, 1951, at the age of 36.

Dr. Lupton was a veteran of World War II, and had contracted rheumatic fever in the tropics, resulting in his hospitalization for more than a year after his return home. He was born in Lewes, Delaware, February 22, 1915, received his A.B. degree from the University of Delaware in 1935, and his M.D. degree from Jefferson Medical College of Philadelphia in 1939. He served a two-year internship at the Philadelphia General Hospital, and later became Demonstrator in Pharmacology on full time at Jefferson Medical College. He later joined the staff of the Hahnemann Medical College and Hospital of Philadelphia, and advanced to the rank of Assistant Professor of Medicine. He was a member of the Philadelphia County Medical Society, the Medical Society of the State of Pennsylvania, and of the American Medical Association. He was elected an Associate of the College in 1950.

DR. JOSEPH IRVING LINDE

Joseph Irving Linde, M.D., F.A.C.P., died on September 15, 1951, at the age of 65, of congestive heart failure. He had a coronary attack in 1948 and had been forced to limit his activities since that time.

He graduated from Yale University School of Medicine in 1908 and practiced pediatrics in New Haven for many years. He was a Diplomate of the American Board of Pediatrics. He had been Clinical Professor of Pediatrics at Yale University School of Medicine. In addition to a great interest in pediatrics, he was greatly interested in public health and, for several years prior to his appointment as Health Officer of New Haven, he had been a member of the Board of Health. In 1936 he was appointed Health Officer of New Haven and was considered one of the superior Health Officers in America. He was a member of the State Tuberculosis Commission and its Chairman for several years. For many years he was Consultant in Pediatrics at the Hospital of St. Raphael and Grace-New Haven Community Hospital. He made many contributions to Connecticut medicine as well as to medicine in the nation. He was elected President of the Connecticut State Medical Society in 1939.

The City of New Haven loses a very efficient Public Health official—the Connecticut State Medical Society one of its most diligent workers—the State of Connecticut a valued member of the Tuberculosis Commission and the doctors of Connecticut a sincere friend and valued counselor.

THOMAS P. MURDOCK, M.D., F.A.C.P.,
Governor for Connecticut

DR. WILFRID JOSEPH COMEAU

Wilfrid Joseph Comeau, M.D., F.A.C.P., of Bangor, Maine, died on September 6, 1951, of coronary occlusion.

He was born in Worcester, Massachusetts, on December 14, 1906. He attended Amherst College, where he received his A.B. degree in 1929. He was graduated from Harvard Medical School in 1933. His postgraduate training began on the second medical service at the Boston City Hospital under the supervision of Dr. Soma Weiss. His interest in cardiology developed early in his career and his early training included service at the House of the Good Samaritan and at the Sanatorium Division of the Boston City Hospital. In 1935 he went to London, England, to study with Dr. Ronald T. Grant as a research fellow at Guys Hospital. The following year was spent at Freiburg, Germany, with Professor Ludwig Ashoff. He then returned to Boston and worked with Dr. Paul White in the cardiac laboratory at the Massachusetts General Hospital until 1939. He then moved to Bangor, Maine, where he entered the private practice of medicine.

Dr. Comeau specialized in Cardiology and made use of his excellent training with considerable benefit to the community in which he lived, to the hospitals with which he was affiliated, and to the numerous local and national organizations to which he belonged. He was senior attending physician at the Eastern Maine General Hospital in Bangor, and was consulting Cardiologist at the Veterans Administration Hospital in Togus, Maine. He served with the Army of the United States as Lieutenant Colonel from 1942–45. He was a member of the Penobscot County Medical Society, the Bangor Medical Club, the New England Heart Association, the American Heart Association and at the time of his death was President of the Maine Heart Association. He was a diplomate of the American Board of Internal Medicine, a diplomate of the National Board of Medical Examiners and a Fellow of the American College of Physicians.

He had contributed numerous publications in the field of cardiology from 1936 to 1951. He had been active in the teaching program at the Eastern Maine General Hospital. He had the ability to think clearly and to convincingly impart his ideas to others. He was a sound clinician who was liked and respected by his associates. His loss is deeply felt by the community in which he served.

RICHARD C. WADSWORTH, M.D., F.A.C.P.,
Bangor, Maine

DR. EDGAR PAUL McNAMEE

Edgar Paul McNâmee, M.D., F.A.C.P., died July 8, 1951, at St. Alexis Hospital, Cleveland, Ohio, where he had been head of the Radiology Department since 1920. Born in Butler County, Pennsylvania, June 29, 1890, Dr. McNamee received his medical degree from the University of Pennsylvania School of Medicine in 1913. Following two years of intern training at the Presbyterian Hospital in Philadelphia, he went to Cleveland to assume charge of the Tuberculosis Dispensary No. 3 of the City of Cleveland. His training in the specialty of Roentgenology began in the Army X-Ray School at Pittsburgh, Pa., in 1917, where as a Lieutenant in the U. S. Army Medical Corps, he served until June, 1919. During World War I, he saw service as a medical officer with the Third Division, during engagements at Chateau-Thierry, St.-Mihiel, and in the Argonne. Returning to Cleveland, he became Roentgenologist in 1920 at St. Alexis Hospital, later becoming Secretary of the Staff and member of its Executive Committee.

The positions in which Dr. McNamee served the medical profession were numerous and varied. He became a Director of the Cleveland Academy of Medicine

from 1938 to 1941, and subsequently, a Councillor of the Ohio State Medical Association, of which, in 1944, he became President-Elect. He served as President in 1946. He became a member of the Board of Directors of the Radiological Society of North America in 1947, acting as its Chairman. He served as Secretary, Treasurer and President of the Cleveland Radiological Society. The American Roentgen Ray Society elected him to membership in 1929. He was a Fellow of the American College of Radiology and a diplomate of the American Board of Radiology. He was Vice-President of the American College of Radiology from 1944 to 1946, and President of the Radiological Society of North America in 1949. He became a Fellow of the American College or Physicians in 1931, a Life Member in 1943, and served actively on the local committees in connection with the 24th Annual Session of the American College of Physicians held in Cleveland in 1940.

Dr. McNamee was not only an acknowledged leader in his special field of interest, he also recognized the social responsibilities of the physician in a day of changing standards and viewpoint. He devoted much of his time to the interpretation of the medical point of view to the lay public, and in his administrative as well as clinical rôles, he did much toward resolving some of the misunderstandings which have been responsible for the friction at times between city, state, and federal governments and the medical profession. His colleagues recognized both his interests and his abilities and trusted him with executive responsibilities both in the State Medical Society and in the Radiological Society of North America.

His passing in his professional prime has left Cleveland and the State of Ohio particularly, and his colleagues at the national level with a deep sense of loss both as a medical statesman and as a personal friend.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. BARTHOLOMEW M. ALLEN

Bartholomew M. Allen, M.D., F.A.C.P., was born in Seaford, Delaware, March 29, 1888, and died unexpectedly at his home in Wilmington, September 7, 1951, following a coronary occlusion.

Dr. Allen attended Seaford High School and the University of Pennsylvania. He received his medical degree from the Medico-Chirurgical College of Philadelphia in 1915. He was intern and resident at the Philadelphia General Hospital, 1915–1917. He served for two years in the Army Medical Corps during World War I and was in general practice in New Castle, Delaware, from 1919 to 1922. In the latter year he moved to Wilmington and began his study of radiology under the late Dr. Daniel Bowen at the Graduate Hospital of the University of Pennsylvania.

After 1925 Dr. Allen devoted his entire time to radiology; since 1927 he was chief radiologist at the Memorial Hospital, Wilmington.

He was a Diplomate, American Board of Radiology, Fellow, American College of Radiology, and, since 1930, a Fellow of the American College of Physicians. Dr. Allen, a former president of the staff of the Memorial Hospital, was a past president of the New Castle County Medical Society, a past president of the Philadelphia Roentgen-Ray Society and at the time of his death was president of the Delaware Academy of Medicine. He served for many years as Consultant in Roentgenology for the E. I. duPont de Nemours and Hercules Powder Companies. His interest in community affairs was shown by his membership in the Wilmington Kiwanis Club, Oriental Lodge No. 21, A.F. & A.M., Delaware Post No. 1, American Legion and the Episcopal Church.

"Bat" Allen was an indefatigable worker who gleaned an amazing amount of information from roentgenological studies which he passed on effectively to the

clinician in the best interest of the patient. He had a vast store of pertinent knowledge and supplemented his reports by word of mouth discussions. He was never too busy to talk to his conferees and truly enjoyed helping younger men in their professional growth. He was an exponent of the finest traditions in medicine and had a remarkable capacity for friendship. His life will continue to be an inspiration to Delaware physicians.

LEMUEL C. MCGEE, M.D., F.A.C.P.,
Governor for Delaware

DR. HAROLD ROBERT CARTER

Dr. Harold Robert Carter, F.A.C.P., Denver, Colo., a native of Michigan, received his B.S. degree from the Emmanuel Missionary College in 1930 and his M.D. degree from the College of Medical Evangelists in 1932. His interneship was served at the Los Angeles General Hospital. His primary field of interest and professional activity was in neurology and psychiatry. His postgraduate work in these fields was done at the Army Medical School, 1938–1939, at the Walter Reed General Hospital between 1939–1941 and later at the Neurological Institute in New York City.

Dr. Carter was retired from the Medical Corps of the Regular Army, with the rank of Captain, in 1943 because of rheumatoid arthritis, following which he entered private practice in Denver. In spite of physical disability, Dr. Carter, in addition to a very active practice, was an important member of the Clinical Faculty of the School of Medicine of the University of Colorado, being an Assistant Clinical Professor of Neurology at the time of his death.

Dr. Carter became a Fellow of the American College of Physicians in 1946. He was a Diplomate of the American Board of Psychiatry and Neurology, a Fellow of the American Academy of Neurology and also held membership in the American Society for Research in Psychosomatic Problems, the Association for the Advancement of Psychiatry and the American Psychiatric Association. He was a member of the American Medical Association, the Colorado State Medical Society and the Medical Society of the City and County of Denver. In connection with his teaching and research interests he was the author of numerous publications in the field of neurology and psychiatry. Dr. Carter died on October 28, 1951, in an automobile accident.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado

DR. HARRY SMITH EMERY

Harry Smith Emery, A.B., M.D., F.A.C.P., Portland, Maine, devoted and beloved physician, died at the age of 79 on October 25, 1951.

He was born January 23, 1872, in Buxton, Maine, the son of Alpheus and Mary Smith Emery. He graduated from Bowdoin College in 1893. In college his fraternity was Alpha Delta Phi. In 1897 he graduated from Jefferson Medical College of Philadelphia, and in 1898 he began the practice of medicine in this city. In the earlier years his practice was general. He was one of the first in his community to specialize in internal medicine and one of the first in Maine to learn and practice the modern treatment of diabetes. From 1914 to 1919 he was instructor in clinical medicine at the Bowdoin Medical School. From 1919 until the school closed in 1921, he was Assistant Professor of Medicine. In 1930 he became a Fellow of the American College of Physicians and later became a Life Member. He served on the attending staff of the Maine General Hospital; later he was a member of the associate staff. He was president of the Cumberland County Medical Society in 1937. In 1947 he was awarded a 50-year medal by the Maine Medical Association.

Dr. Emery will be remembered by his former patients as an unselfish physician worthy of the vast confidence they felt in him. He will be remembered by his colleagues as a careful diagnostician and as a consultant who never failed to bring a fresh point of view and new light into every difficult situation.

RICHARD S. HAWKES, M.D., F.A.C.P.,
Governor for Maine

DR. ALFRED W. GRAY

Dr. Alfred W. Gray, A.B., M.D., F.A.C.P., died at Columbia Hospital, Milwaukee, Wisconsin on June 24, 1951.

Dr. Gray was the last of three generations of Milwaukee physicians. His grandfather came to Milwaukee in 1856 from Jamestown, N. Y. Besides practicing medicine, he preached in Presbyterian churches in Jamestown and Milwaukee. Dr. Gray's father, Nathaniel A. Gray, began practicing in Milwaukee in 1867.

Dr. Gray was born in 1874. He received his A.B. degree from the University of Wisconsin in 1895 and graduated from Columbia University College of Physicians and Surgeons in 1899.

After graduation, Dr. Gray returned to Milwaukee and entered into practice with his father. During his early years of practice, Dr. Gray devoted most of his time to pediatrics, and was one of the organizers of the Milwaukee Infant Hospital. After many years of excellent service, this institution was united with the Milwaukee Children's Hospital. Dr. Gray was also one of the founders of Columbia Hospital and was a member of the staff at the time of his death.

In his early days, Dr. Gray served as secretary and president of the Medical Society of Milwaukee County and was President of the Milwaukee Academy of Medicine.

During World War I, he held the rank of major in the Army Medical Corps and was stationed at Camp Grant.

Later in his career, Dr. Gray became active in industrial medicine, with especial interest in the recognition of early silicosis and the influence upon the present and future disability of the exposed worker. At this time, in 1934, relatively little was known about the signs and symptoms of early silicosis, and Dr. Gray's intensive interest and study of these cases went far to give a better understanding and greater clarification of this preventable condition.

As a physician, Dr. Gray was an idealist but at the same time was sufficiently realistic to recognize that every patient was an individual and that the treatment of the individual was very frequently more important than the condition producing the symptoms. Toward his patients he was kind and sympathetic, with the result that they invariably became devoted to him. The physicians of the community admired his personality and respected him for his ability and knowledge. Perhaps slightly inclined toward the more serious side of life, at the same time he was an enthusiastic golfer and enjoyed a good story and the company of his friends. He is survived by his wife, Ada Ferry Gray.

OSCAR LOTZ, M.D., F.A.C.P.

DR. DAVID BALDWIN JEWETT

David Baldwin Jewett, M.D., M.S., Rochester, N. Y., was born May 29, 1880, and died July 12, 1951, from coronary thrombosis.

He was born in Rochester, N. Y., and graduated from Trinity College, Hartford, Conn. In 1902 he received his M.D. degree from the New York Homeopathic Medical College and Hospital. He served for many years in the capacity of Physician for the Outpatient Department, Attending Physician and Medical Director of the

Rochester Homeopathic Hospital. Until his retirement from practice in 1950, he was Consultant in Medicine at Strong Memorial-Rochester Municipal Hospitals. He was Honorary Director of the Medical Department of the Genesee Hospital and Consulting Physician to the Newark State School, Gowanda State Homeopathic Hospital (Helmuth) and Monroe County Infirmary. A Diplomate of the American Board of Internal Medicine, he received the honorary degree of Master of Science from Trinity College.

Dr. Jewett had been a Fellow of the American College of Physicians since 1926. He was past President of the Rochester Academy of Medicine and was very active in the progress of its library. The Rochester Academy of Medicine honored Dr. Jewett as a Life Member, and the library is dedicated as the "David B. Jewett Library" as a tribute to his great love of medicine.

During World War I Dr. Jewett served as a Captain in the Medical Corps, U. S. Army. He was considered by his associates to be an excellent teacher, clinician and friend.

The death of Dr. Jewett brought sorrow to his many friends and patients in Rochester, and he will be missed by them. He is survived by his wife and children.

EDWARD C. REIFENSTEIN, Sr., M.D.,
Governor for Western New York

DR. PEDRO L. FARIÑAS MAYO

Pedro L. Fariñas Mayo, M.D., F.A.C.P., Havana, Cuba, died suddenly on April 26, 1951, of coronary thrombosis, at the age of 59. Dr. Fariñas was born in Santa Clara, Cuba, October 19, 1892.

He received his B.A. degree in that city in 1912 and his M.D. degree from the University of Havana in 1917. While a senior medical student, he began as an assistant in the Department of Radiology at Quinta de Dependientes, where he received a scholarship for the study of Roentgenology in foreign centers. Soon he became head of that Department, initiating his career with rapid success. Shortly after he was appointed Radiologist to the Calixto Garcia Hospital (later University Hospital) which he served until his death, with marked skill. In addition, he had been head of the Department of Radiology at the Women's Hospital, Consultant to the Maternity and Children's City Hospitals, Institute of Cancer, etc.

Dr. Fariñas held numerous offices in medical societies. He was President of the Section on Radiology at the IV Pan-American Meeting at Dallas, 1933; Honorary President of the Section at the International Congress of Radiology, Chicago, 1937; Founder and first President of the Latin-American College of Radiology, Chicago, 1937; President of the Second Inter-American Congress of Roentgenology, Havana, 1946; Vice President of the Sixth International Congress of Radiology, London, 1950; President of the Cuban Chapter of the Pan-American Medical Association and of the American College of Chest Physicians.

He held membership in the following: Academy of Sciences, Society of Clinical Studies of Havana, the Cuban Society of Radiology and Physiotherapy, American Heart Association, American Trudeau Society and others. He was an honorary member of the Cuban Societies of Cardiology and of Urology, Mexican Society of Radiology and Physiotherapy, Medical Society of the General Hospital, in Mexico, the Radiological Societies of Argentina, Colombia, Peru, and Venezuela. He was a Fellow and later Honorary Fellow of the American College of Radiology, a corresponding member of the Mexican Academy of Medicine and of the Buenos Aires Society of Internal Medicine. He had been a Fellow of the American College of Physicians since 1941.

Dr. Fariñas organized many postgraduate courses in Radiology such as at the

University of Mexico in 1933 and 1940, and at the University of Havana during the Summer School several years. He gave a refresher course at a meeting held in Boston in 1940 by the American Roentgen Ray Society; he was President and organizer of a postgraduate course on chest diseases, for the Cuban Chapter of the American College of Chest Physicians, and a course on Internal Medicine, for the Cuban College of Physicians. He was a hard worker and a very prolific writer in his specialty, have published some 112 articles, covering a great variety of subjects. His work was largely confined to Roentgenology. His writings revealed his great originality such as in his paper, "Bronchography in Bronchial Carcinoma" (with Professors P. A. Castillo and C. Basterrechea), and his paper on "Aortography."

Dr. Fariñas was a man of great resourcefulness and executive ability. In addition to his society and hospital activities, for which he won general recognition, he was always very active in the private practice of Roentgenology, through which he achieved special prominence. He was honored as Extraordinary Professor by the University of Mexico, given the title of Eminent and Distinguished Son of Santa Clara, the city where he was born. He received the degree of Comendador in both the National Orders of Merit, Carlos Manuel de Céspedes and Carlos Finlay, by the Cuban Government. He was a masterful clinical roentgenologist with a profound knowledge of the fundamentals of medical science and had wide clinical experience that made him an extraordinary consultant in radiological diagnosis. He performed great service to his country and to the progress of science. The medical profession of Cuba has suffered a great loss. He will be long remembered by our leaders in medicine for his great coöperative attitude, and he will never be forgotten by the younger ascending generation of physicians for his great contributions to the diffusion of knowledge.

José J. Centurión, M.D., F.A.C.P.,
Governor for Cuba

DR. SAMUEL WATKINS SAPPINGTON

On May 16, 1951, Dr. Samuel Watkins Sappington died at his home in Bryn Mawr, Pa., at the age of 77 years.

After graduating in medicine from Hahnemann Medical College and Hospital of Philadelphia in 1897, Dr. Sappington secured additional training in Vienna, London and Berlin. On returning to Philadelphia he soon entered upon a long and distinguished academic career at the Hahnemann Medical College and Hospital of Philadelphia. Beginning this association as Demonstrator in Pathology in 1900, he quickly rose in rank and became Professor of Pathology in 1907. At the time of his death he was the beloved and respected Emeritus Professor of Pathology at his alma mater.

Dr. Sappington was a Founding Fellow of the College of American Pathologists and a Diplomate of the American Board of Pathology. He became a Fellow of the American College of Physicians in 1930.

Thomas M. McMillan, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. CALEB ODHELIUS TERRELL

Dr. Caleb Odhelius Terrell, Fort Worth, Tex., died of nephrosclerosis, July 28, 1951.

He was born in Ranger, Tex., on August 11, 1888. He received his M.D. degree from the University of Texas Medical Department in 1910. He served an internship at St. Mary's Hospital, Galveston, and a residence at St. Joseph's Hospital in Houston. During World War I he served in the Army Air Force and was discharged with the

rank of Captain. In 1922 he did postgraduate work, in pediatrics, at Harvard Medical School and at Washington University School of Medicine, St. Louis, and served a residency at the Children's Hospital, Iowa City, Iowa. He then moved to Fort Worth, where he specialized in pediatrics.

Dr. Terrell was a member of the Tarrant County Medical Society, the Texas Medical Association, the American Medical Association, the Southern Medical Association, the American Academy of Pediatrics, the Texas Pediatric Society, and the Fort Worth Pediatric Society. He had been President of Tarrant County Medical Society and Secretary of the Section on Medicine and Diseases of Children, and Chairman of the Section on Pediatrics, Texas Medical Association.

Dr. Terrell served as a member of the State Board of Medical Examiners. He was a member of the Board of Regents of the University of Texas from 1944 until 1951. He was a Diplomate of the American Board of Pediatrics and a Fellow of the American College of Physicians, having been elected in 1936.

Dr. Terrell served his patients, his profession, his alma mater and his state faithfully and efficiently for many years.

D. W. Carter, Jr., M.D., F.A.C.P.,
Governor for Texas

DR. PAUL HENRY WOSIKA

Dr. Paul Henry Wosika, F.A.C.P., Chicago, Illinois, died on September 8, 1951, in the crash of his private airplane near Crete, Illinois. This tragic ending of his life was a great shock to his many friends, patients and acquaintances.

Dr. Wosika was born in Oklahoma City, Oklahoma, June 12, 1905. He received his M.D. degree from Northwestern University Medical School in 1931 and subsequently received his M.S. (1936) and his Ph.D. (1941) in Medicine from the same University. He served an internship and a residency in medicine at Passavant Memorial Hospital, Chicago. He was also a house officer at the Peter Bent Brigham Hospital in Boston. It was at the Brigham where Dr. Wosika came under the influence and guidance of the late Dr. Henry A. Christian, M.A.C.P., who had much to do with the molding of Dr. Wosika's high ideals of practice.

From 1934 to 1942, Dr. Wosika held various fellowships and instructorships at Northwestern University Medical School. In 1942 he became Associate Professor of Medicine at the Chicago Medical School and held this position until the time of his death. Since 1942 he had been an Attending Physician at the Illinois Masonic Hospital and President of the Medical Staff there at the time of his demise. He was also a Consultant to the Cook County Infirmary at Oak Forest.

Dr. Wosika was a Fellow of the American Medical Association, a member of his county and state medical societies and had been a Fellow of the American College of Physicians since 1947, and a Life Member since 1948. He was also a member of the Central Society for Clinical Research, the American Federation for Clinical Research, Chicago Society of Internal Medicine, and a Diplomate of the American Board of Internal Medicine. He was also a Mason, having received the 33rd degree at Philadelphia on September 27, 1950.

Dr. Wosika was the author of numerous papers dealing with cardiovascular disease and internal medicine, and was co-author with Dr. Chauncey Maher, of Chicago, of a textbook on Electrocardiography.

He was a brilliant, hard-working internist who was devoted to his patients and to clinical investigation. During all of his professional years he had contributed richly. His tragic death is a shock to his community and a great loss to his patients, to his friends and his devoted parents.

Howard Wakefield, M.D., F.A.C.P.,
Governor for Illinois

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